# Microwave heating
# in fine chemical applications:

## role of heterogeneity

Proefschrift

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| | |
|---|---|
| BINAP | 2,2'-BIs(diphenylphosphino)-1,1'-biNAPhthyl |
| C | Cooler |
| CALB | *Candida antartica* lipase B |
| CFR | Continuous-flow reactor (FlowSYNTH) |
| CH | Conventional heating |
| CLEA | Cross-linked enzymatic aggregate |
| $c_P$ | Heat capacity |
| CSTR | Continuous stirred tank reactor |
| DKR | Dynamic kinetic resolution |
| DMA | *N,N*-Dimethylacetamide |
| $d_P$ | Penetration depth |
| EDTA | Ethylenediaminetetraacetic acid |
| ee | Enantiomeric excess |
| $f_{MW}$ | Microwave effect |
| HDI | Hexamethylenediisocyanate |
| HI | Hexylisocyanate |
| MTBE | Methyl *tert.*-butyl ether |
| MW | Microwave (heating) |
| NMP | *N*-Methylpyrrolidinone |
| PEEK | Polyetheretherketone |
| PPL | *Porcine Pancreas* lipase |
| R | Reactor |
| $(r_{MW})_{t=0}$ | Initial reaction rate for microwave heating |
| rt | Room temperature |
| RTD | Residence time distribution |
| T | Temperature (sensor) |
| tan δ | Loss tangent |
| Teflon | Poly(tetrafluoroethylene) (*Brand name of DuPont*) |
| THF | Tetrahydrofuran |
| Upy | Ureidopyrimidinone |
| Weflon | Teflon incorporated with carbon (25 % wt) |
| $\Delta_{soln}H°$ | Heat (enthalpy) of solution |
| $\varepsilon'$ | Dielectric constant |
| $\varepsilon''$ | Dielectric loss |

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# Chapter 1

# 1

## Introduction

# Abstract

Microwave or dielectric heating is an accepted new technique to run chemical conversions on a lab scale as an alternative heating principle.

Microwave heating is believed to be more depending on the molecular properties and the reaction conditions than conventional heating.

At first sight microwave-assisted chemistry looks very promising given the overwhelming number of publications during the last two decades. To predict its potential for industrial purposes, it is necessary to make a proper comparison between both heating techniques.

The underlying theory, "Green Chemistry" and the microwave effect are relevant topics to be studied in detail in nowadays' organic chemistry.

According to literature microwave-assisted chemistry seems to perform well and sometimes it even works better than expected. Magic or hidden logic?

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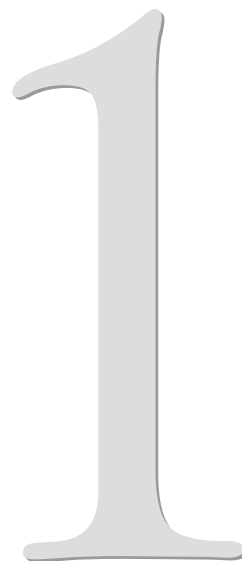
## 1.1 Changing chemistry

Melting a chocolate candy bar in your shirt seems to be an undesired side effect of the application of microwaves in its early period. Although microwaves were applied for RADAR purposes, these electromagnetic waves were also able to heat up all kinds of materials. Recognition of this relationship has brought the microwave oven eventually into most of our kitchens. The ability to heat is maybe the most important primary tool for mankind. This is no exception in the fume hood of today's organic chemist. Open fire is rarely used anymore for safety reasons. The oil bath succeeds as a common heating tool. But where does the microwave oven fit in the picture of performing organic chemistry?

The first papers on microwave-assisted organic chemistry date back to 1986. Till around the year 2000 a number of experiences with this technique have not always been so successful, due to uncontrolled conditions. The combination of a domestic microwave oven and combustible solvents made the heating device for single use only. Safety in this case was also a good reason to improve the heating technique. More reliable equipment with proper control over temperature and pressure are standard in modern times.

Since then the acceptance of this novel heating tool has increased enormously in many laboratories all over the world. Especially on a small scale (< 5 mL) the microwave oven is used extensively and this created the necessity to make it suitable for automation. This occurred almost simultaneously with the introduction of combinatorial chemistry and parallel synthesis in the pharmaceutical industry where fast innovation, to find new blockbusters, was desired. The strong growth in the number of scientific articles shows that the microwave oven can be put into practice for all kinds of chemical transformations.[1] The application of microwave heating has not, however, penetrated yet as a standard tool into the fine chemical industry for the production beyond the 10 kg level. Nonetheless, large equipment is already available and is in use by the food processing or ceramic industry. This brings us to address the scaling-up potential of microwave-assisted chemistry.

## 1.2 Microwave-assisted chemistry

Although the use of a domestic oven without control of temperature has been described in a large number of papers, this premature approach does not affect the

widespread application of microwave heating throughout numerous types of chemical transformations. It is nearly a Herculean effort to give a complete overview where microwave heating has been applied to heat up chemical reactions.[2-16] Even below room temperature microwave irradiation is used to run a reaction in combination with simultaneous cooling.[17,18]

One of the first reactions described is the hydrolysis of benzamide in aqueous sulfuric acid (see Scheme 1.1).[19] The use of polar components facilitates the absorption of microwave energy and consequently the conversion into heat. With the use of a sealed vessel it was possible to increase the temperature and eventually the pressure and therefore reaction rates. The reduction of reaction time and the growth in chemical yield were seen as the advantages of microwave heating.
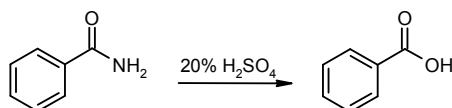


**Scheme 1.1**    *Hydrolysis of benzamide in aqueous sulfuric acid.*

Working in aqueous media or applying solid-phase chemistry ("dry-media") were possible solutions to prevent explosion in the domestic machines. This way of working was later recognized as one way of "Green Chemistry".

**Green Chemistry.** *Based on a report (Our Common Future, 1987) from United Nations World Commission on Environment and Development (WCED)[20] sustainability was acknowledged as an important development. "Green Chemistry" is a science-based, non-regulatory, economically driven approach toward sustainable development.[21-23] This advance has led to a program supported by U.S. Environmental Protection Agency, including a Presidential Green Chemistry Challenge Award since 1996. Later the twelve principles were added to bring theory into a more practical perspective, see Table 1.1.*

**Table 1.1**    *The twelve principles of "Green Chemistry" by U.S. Environmental Protection Agency.*

| Principles of "Green Chemistry" | | | |
|---|---|---|---|
| No | | No | |
| 1 | Prevent waste | 7 | Maximize atom economy |
| 2 | Design safer chemicals and products | 8 | Use safer solvents and reaction conditions |
| 3 | Design less hazardous chemical syntheses | 9 | Increase energy efficiency |
| 4 | Use renewable feedstock | 10 | Design chemicals and products to degrade after use |
| 5 | Use catalysts, not stoichiometric reagents | 11 | Analyze in real time to prevent pollution |
| 6 | Avoid chemical derivatives | 12 | Minimize the potential for accidents |

However, the chemical reaction itself is only a small part of the entire process to obtain products pure. In many cases work-up is more laborious and waste producing than the chemical conversion itself (*e.g.* extractions or pH-shifts). The overall greenish color is, therefore, questionable. The energy consumption is another parameter to determine whether microwave heating is environmentally friendly.

In 1986 several Diels-Alder reactions (*e.g.* see Scheme 1.2) were investigated in the microwave oven.[24] The paper demonstrates nicely the struggle to make microwave irradiation suitable for organic chemistry, involving smart solutions to measure the temperature inside the oven and even including an example of an exploding reaction vessel.
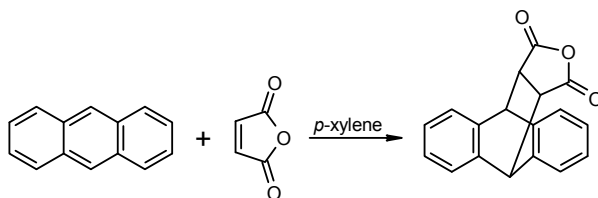


**Scheme 1.2**    *A Diels-Alder reaction of anthracene with maleic anhydride.[24]*

Two additional attractive areas to study microwave heating have been biocatalysis and the application of ionic liquids. Both, classified under "Green Chemistry", were expected to show synergy with microwave heating.[25,26] Important factors to work with ionic liquids are their high boiling points and low volatility. Extremely fast heating rate curves (up to 10 °C per second) are observed for ionic liquids under microwave irradiation, due to the presence of ions which strongly interact with the electromagnetic waves. Scheme 1.3 shows a Heck reaction performed in an ionic liquid as an example.[27]
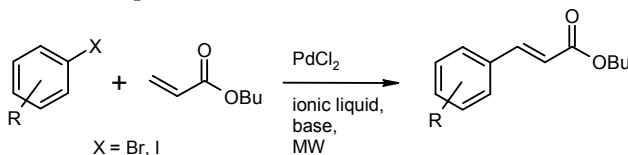


**Scheme 1.3**    *Heck reaction in an ionic liquid heated by microwave irradiation.*

Also the synthesis of ionic liquids is very successful with microwave technology. A recent example from supramolecular chemistry applications is depicted in Scheme 1.4. This is a typical publication which demonstrates the possibility of a successful switch to an alternative heating source, albeit with lack of accurate reaction/temperature control by using a domestic oven.[28] A critical view is necessary to make a fair comparison with conventional heating. This point needs to

be addressed in which reaction conditions are really comparable. Independent on the reaction conditions (*e.g.* heterogeneous *vs.* homogeneous mixtures or open *vs.* closed systems) a correct temperature measurement of the reaction mixture has to be ensured. The absence of temperature control or the usage of domestic ovens (multi-mode machine, see chapter 1.4) till 2001 characterized the majority of published microwave-assisted chemistry. Non-stirrable reaction mixtures (*e.g.* solvent-free conditions with a high percentage of solids) in a microwave oven give irreproducible results upon duplication or lead to misinterpretation when compared with the conventionally heated experiments.
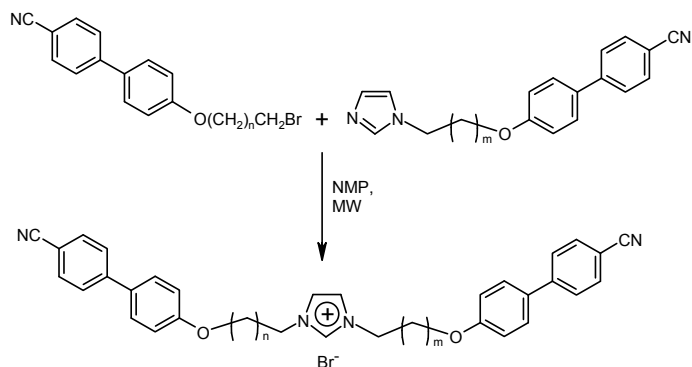


**Scheme 1.4** *Formation of an ionic liquid by microwave irradiation.[28]*

## 1.3 Microwave irradiation[29]

Dielectric heating is a means of transforming electromagnetic energy into heat. This transformation depends on the properties of the molecules and the conditions. Different molecules may display different effects. Domestic and industrial microwave ovens are required to operate in general at wavelengths of either 12.2 cm (2.45 GHz) or 33.3 cm (900 MHz). The other frequencies (from 300 MHz to 300 GHz) are used for RADAR transmission or telecommunication. All reactions in this thesis or in the list of references were operated at 2.45 GHz. This corresponds to an energy of the microwave photon of approximately $10^{-5}$ eV, which is unable to break any (hydrogen-)bonds, see Table 1.2 and Figure 1.1.

In liquids and solids, where molecules are generally not free to rotate independently, the microwave spectra of molecular rotation are too broad to disclose relevant information for analytical purposes. It is to these phases of solid and liquid that microwave heating effects originating from dielectric loss (see also next pages) are relevant and need to be distinguished from the spectroscopically relevant effects.
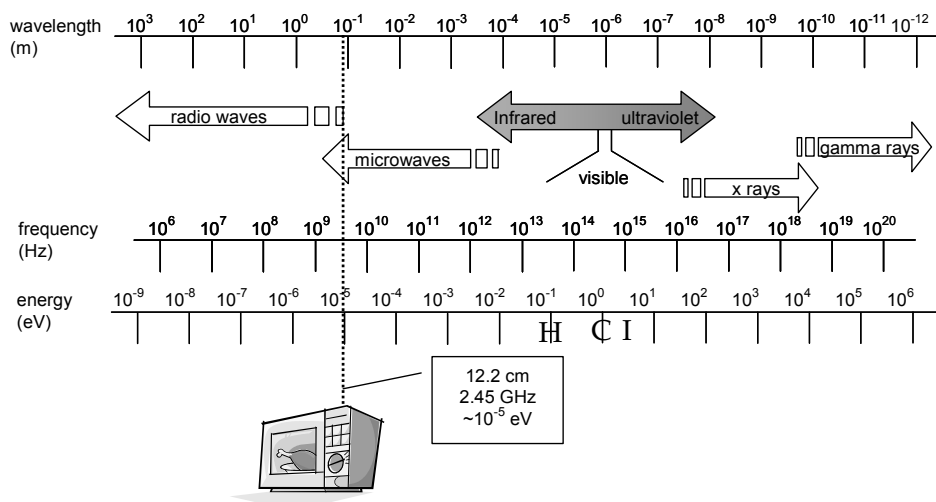
**Figure 1.1** *Electromagnetic spectrum, the microwave oven and molecular bonds (hydrogen [H], covalent [C] and ionic bond [I]).*

**Table 1.2** *Energy of various intermolecular bonds in comparison to the energy of a microwave photon.*

|  | Microwave photon (2.45 GHz) | Hydrogen bond (H)* | Covalent bond (C)* | Ionic bond (I)* |
|---|---|---|---|---|
| Energy (eV) | ~$10^{-5}$ | ~0.04 to 0.44 | ~3.82 (C-C) | ~7.6 |

\* intermolecular bonds are also depicted in Figure 1.1 with the corresponding letters H/C/I.

Heating relies on the ability of an electric field to polarize charges and the inability of these charges to follow rapid reversals of an electric field. (Dielectric) polarization is the sum of multiple types of polarizations, see Equation 1.1.

$$\alpha_t = \alpha_e + \alpha_a + \alpha_d + \alpha_i \tag{1.1}$$

$\alpha_t$ = *total polarization*
$\alpha_e$ = *electronic polarization*
$\alpha_a$ = *atomic polarization*
$\alpha_d$ = *dipolar polarization*
$\alpha_i$ = *interfacial polarization*

Electronic polarization arises from the alignment of electrons around specific nuclei. Atomic polarization results from the relative displacement of nuclei due to the unequal distribution of charges within the molecule. Dipolar polarization results from the orientation of permanent dipoles by the electric field while

interfacial polarization (Maxwell-Wagner effect) occurs when there is a build-up of charges at interfaces. The first two (electronic and atomic) polarization effects are much faster than the microwave frequencies and, therefore, these effects do not contribute to the dielectric heating effect.

Successively to electronic and atomic polarization, dipolar polarization (in the range of microwave frequencies) results in polarization of dipoles which lags behind the changes of the electric field. The lag indicates that the sample absorbs energy from the field and is heated. Two parameters define the dielectric properties of materials; dielectric constant ($\varepsilon'$) and dielectric loss ($\varepsilon''$). The first parameter indicates the ability of a molecule to be polarized, the second one gives insight in the efficiency of converting radiation into heat. The ratio of these quantities ($\varepsilon''/\varepsilon'$) is the loss tangent (= tan $\delta$). The loss tangent defines the ability of a material to convert electromagnetic energy into heat energy at a given frequency and temperature (see Table 1.3).

**Table 1.3** *Loss tangent of several liquids/materials*

| solvent | loss tangent [a] | solid/liquid | loss tangent (temperature) |
|---|---|---|---|
| ethylene glycol | 1.350 | | |
| ethanol | 0.941 | ice | 0.00027 (0 °C) [d] |
| DMSO | 0.825 | water | 0.207   (0 °C) [b] |
| methanol | 0.659 | water | 0.123   (20 °C) [a] |
| NMP | 0.275 | water | 0.097   (25 °C) [b] |
| acetic acid | 0.174 | water | 0.056   (50 °C) [b] |
| water | 0.123 | | |
| chloroform | 0.091 | **material** | loss tangent [c] |
| tetrahydofuran | 0.047 | | |
| dichloromethane | 0.042 | | |
| toluene | 0.040 | Teflon | 0.00028 |
| hexane | 0.020 | fused quartz | 0.00006 |

*a: 20 °C, 2.45 GHz [reference 30]; b: 2.0 GHz [reference 31]; c: 20 °C, 3 GHz [reference 32]; d: 2.45 GHz [reference 33]*

For example within interfacial polarization, a suspension of conducting particles in a non-conducting medium is a heterogeneous mixture whose dielectric constant is frequency dependent. The loss relates to the build-up of charges between the interfaces. Its importance in the microwave region has not been well-defined. Absorption centered around a frequency of $10^7$ Hz may tail into this frequency range. For highly electrical conductive liquids and solids a point is reached where

the conductive loss effects are larger than the dipolar relaxation effects (large amount of salts, high temperature).

The final temperature rise is determined by the loss tangent, specific heat capacity, emissivity of the sample and the strength of the applied field. All these properties are temperature dependent. As the composition of the reaction mixture develops with time, all interactions with microwave irradiation will also change. This makes the complete system very dynamic. The loss tangent is also determining the penetration depth of microwaves into the reaction mixture. For water as a medium microwave absorber the penetration is only a few centimeters. This limitation is a determining factor to assess the scaling-up of batch processes.

**Microwave effect**

By studying microwave irradiation it is impossible to leave the discussion about microwave effects untouched. In the scientific world the microwave effect is a collective noun for all the positive contributions to reaction rate enhancement which microwave irradiation has brought up. In most cases there is a lack of fair comparison between or good control of reaction conditions. Attempts to reproduce reactions claiming beneficial microwave effect have mostly led to a reasonable explanation, namely higher temperatures.[34,35] The overview of all claimed microwave effects can simply be divided into two basic parts: thermal and non-thermal.[36-38]

Good temperature control during the reaction and a known heating profile will preclude the existence of most non-thermal effects on a macroscopic scale (see Figure 1.2),[16] although the heating rate in some cases is irreproducible during conventional heating.



claims*
oil bath        : 55 % (65 °C, 4 h)
MW (15 W): 89 % (48 °C, 4 h)

re-evalution**
oil bath        : 79 % (65 °C, 5 h)
MW (7 W)  : 83 % (65 °C, 5 h)
MW (57 W): 81 % (65 °C, 5 h)
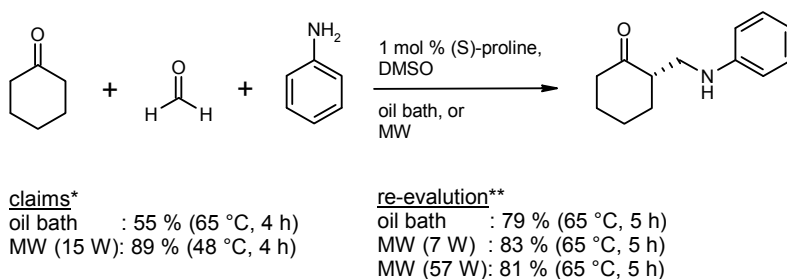
**Figure 1.2**    *Asymmetric Mannich reaction.*
              *  [reference 39], reaction at constant MW power*
              *** [reference 16], reaction at constant temperature*

This could erroneously be interpreted as a non-thermal effect. Overheating can also be observed under special conditions. Due to the absence of nucleation, boiling

points of pure solvents can increase up to thirty degrees.[40] This increase in temperature can influence reflux conditions depending on the heating mode. In other words reflux conditions under microwave heating with a high power input induce a higher conversion rate as compared to a conventionally heated experiment under reflux conditions. Likewise proper temperature control will reveal the presence of a thermal effect.

Any unexplainable effects are almost automatically transferred to the non-thermal part. This is also the part which embraces many speculations and theories. The debate is currently ongoing and the field can be divided into two camps: those who advocate the existence of non-thermal effects and those who accept only purely thermal effects as explanation.

## 1.4 Microwave equipment

The principle how a microwave oven works is beyond the scope of this study, but basically a microwave oven is a thermionic diode (an anode combined with a directly heated cathode).[12,29,41-44]

Two types of microwave reactors are nowadays available for the organic chemist: mono-mode (single-mode) and multi-mode. The mono-mode machines have a cavity which is designed for one vessel only. The electromagnetic beam is focused and its optimum is located in the centre of the reaction vessel. This type of equipment has demonstrated to be ideal in an explorative environment with the possibility for automation. CEM Corporation is market leader in this field (Figure 1.3). Other providers of laboratory dedicated microwave ovens are Biotage, Milestone and Anton-Paar.

(a)                    (b)                    (c)                              (d)
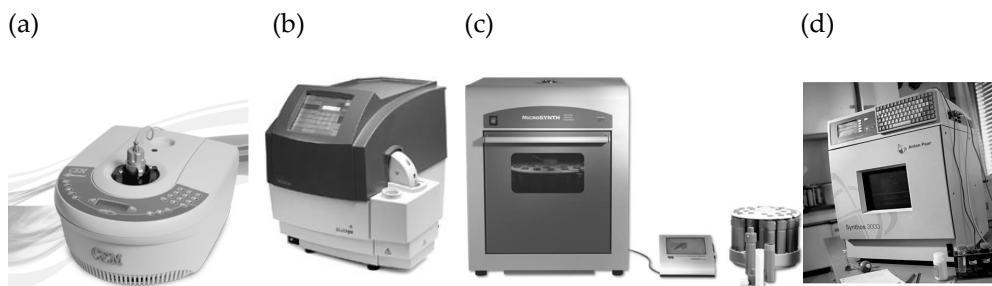


**Figure 1.3**    *Mono-mode microwave ovens from (a) CEM, (b) Biotage and multi-mode microwave ovens from (c) Milestone, (d) Anton Paar.*

The limitation of the mono-mode machine is the lack for proper scaling-up potential. The sizes of the cavity remain rather small in dimensions and technical solutions within this area of interest are not available. This brings us almost automatically to the other type, namely the multi-mode microwave oven.

In principle both types have a magnetron which produces the electromagnetic waves. These waves are emitted by an antenna indirectly into the cavity which holds room to perform some chemistry as in the ordinary domestic models. In the case of a multi-mode the waves are scattered with a mode stirrer throughout the cavity (which is considerably larger than the mono-mode). Reflection against the walls and extinction or amplification inside the cavity may occur. This is not ideal for small samples, but it creates room for larger perspectives such as either vessels or incorporation of a continuously operated setup. Either normal glassware, quartz or PTFE reactors can be inserted into the cavity in combination with stirring and temperature control by an internal fiber optic device, gas-pressure sensor or an infrared sensor. The boundaries of performance are 300 °C and 100 bar for some setups. The suppliers in this market (including mono-mode) are limited, see Figure 1.4.
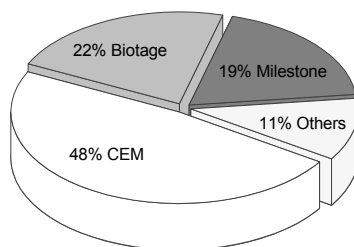


Source: Evalueserve Analysis

**Figure 1.4**    *Market share (by revenues; 100% equals $ 89m) of manufacturers in 2003.*

## 1.5 Aim of the thesis

The aim of this thesis is to assess microwave heating as a novel technique for scaling-up fine chemical processes. Heterogeneous processes are initially studied batchwise to clarify the performance of microwave heating in terms of conversion rate and selectivity through a direct comparison with conventional heating. The results obtained allow eventually to elucidate the existence of beneficial microwave

effects demonstrating its added value in process research. It would facilitate the study on the feasibility of a microwave oven integrated fume hood setup for producing larger volumes of fine chemicals.

## 1.6 Outline of the thesis

Multiple reactions are explored either known from the literature or from industrial practice and are discussed in chapter 2. In all cases the conversion and the selectivity of the particular chemical reaction were studied in order to determine the degree in which the performance of microwave heating differs from the conventional method of heating. In particular biocatalysis has been considered to be a promising methodology to overcome the necessity of heavy metals in catalysis and to demonstrate selectivity in a chemical conversion. All reactions were claimed to involve reaction rate enhancements and, therefore, positive microwave effects. The heterogeneous character is discussed in relationship to the microwave effect in view of the results described in chapter 3 and 4.

In chapter 3 the racemization of *N*-acetyl amino acids is emphasized as part of a fine chemical process to recycle the undesired enantiomer. Structural variations are introduced to extend the application of a beneficial microwave effect to other analogues.

In chapter 4 the nucleophilic addition of a series of isocytosines to a mono and a di-isocyanate is discussed. In the latter case ureidopyrimidinone serves as a precursor for monomers which give rise to hydrogen-bonded supramolecular polymers. By introducing a series of substituted isocytosines the influence of heterogeneity on the difference between microwave and conventional heating can be deduced. The observations contribute to the predictability of a microwave effect.

In chapter 5 the continuous-flow reactor is introduced as a logic approach to scaling-up microwave-heated processes. A feasibility study is performed in which for practical reasons the reactor is short-circuited into a batch-loop reactor. Energy and mass balances are discussed in combination with the performance and limitations of this setup. The introduction of a fume hood concept describes the opportunity to produce actual end products under microwave-heated flow conditions, *i.e.* a mini-plant.

In chapter 6 the actual performance of the batch-loop reactor regarding chemical conversion and selectivity is elucidated. Four processes showing different behavior under microwave irradiation give insight into the viability of fine chemical applications.

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# Chapter 2

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# Heterogeneous vs. homogeneous systems:

## Re-evaluation of reactions holding a microwave effect claim

# Abstract

Several heterogeneous reactions, for which microwave effects are claimed, have been re-evaluated.

Biocatalyzed (trans)esterifications were performed under standardized conditions and this showed similar time - conversion histories and selectivities for both, microwave or conventional heating.

In the piperidine/piperazine formation from 1,5-dibromopentane or bis(2-chloro-ethyl)amine.HCl the observed rate enhancement with microwave heating was completely counterbalanced by proper temperature control.

The oxidation of benzyl alcohol with iron(III)-nitrate to benzaldehyde was studied in detail. This led to the observation of identical reaction rates when conventional heating was substituted by microwave heating. Also the heterogeneous Williamson synthesis of methyl gallate with dodecyl bromide afforded identical reaction rates for both heating techniques.

In the only industrially applied, scaled-up process - the Laurydone synthesis, transforming pyroglutamic acid into its decyl ester - vigorous stirring guaranteed a homogeneous temperature distribution in the reactor. With this approach the claimed microwave effect vanished.

In the aforementioned process types the claims regarding rate enhancement by microwave heating have been rationalized by differences in reaction temperature. However, the results also suggest that heterogeneity in itself may have profound influence on the rate of microwave-heated experiments.

## 2.1 Introduction

Reaction systems are either heterogeneous or homogeneous. In view of space-time volume efficiencies, high concentrations are preferred over dilute reaction conditions. Chemical reactions tend to run faster when all components are dissolved to the same extent. Liquids handling is generally less complicated than solids handling, but the latter is not an insurmountable obstacle. Safety issues may, however, require dilute reaction mixtures. Unfortunately, there is no general rule to perform chemical reactions. Statistically, heterogeneous reactions are involved in the majority (> 75 %)[1] of fine chemical processes. Associated with the chemical reaction is the work-up of the reaction mixture. The more undesired components are introduced, the more effort is needed to remove these components, *e.g.* also the removal of additional solvent by distillation. All together our attention will mainly be focused on heterogeneous reaction systems.

## 2.2 Heterogeneous reaction systems

Roughly the group of heterogeneous reaction systems can be divided into three categories: solid-liquid, liquid-liquid or gas-liquid (Figure 2.1; other combinations or multiple (> 2) phases will not be addressed). Each category will be discussed in various sections of this chapter (Table 2.1).
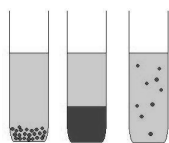


**Figure 2.1**    *Heterogeneous systems; solid-liquid, liquid-liquid and gas-liquid.*

**Table 2.1**    *Subdivision of heterogeneous reactions discussed in this chapter.*

| entry | heterogeneous system* | reaction type | |
|---|---|---|---|
| 1 | solid-liquid | *Biocatalysis (2.3)* | *Laurydone process (2.7)* |
| | | *Williamson synthesis (2.6)* | |
| 2 | liquid-liquid | *Piperidine formation (2.4)* | *Oxidation of benzyl alcohol (2.5)* |
| 3 | gas-liquid | *Piperazine formation (2.4)* | |

\* *This subdivision is based on initial reaction conditions*

Each of these three combinations needs appropriate mixing to ensure efficient contact between the reactants. Mass transfer limitation may strongly influence the

reaction rates. If the interfacial area is enlarged to decrease the resistance against mass transfer, the reaction time is reduced in most cases.

The ultimately desired combination is to operate a concentrated mixture with high reaction rates under safe conditions. How good is the fit of the involved parameters (*e.g.* temperature, time or concentration) with the setup of a continuous-flow reactor heated by microwave irradiation compared to conventional methods? Before answering this question our research was initiated with a number of heterogeneous chemical reactions to validate the occurrence of any beneficial (microwave) effects which had been claimed in literature reports.

## 2.3 Biocatalysis

Our life should not exist without biocatalysis (*i.e.* catalysis by enzymes). In an organism enzymes catalyze numerous processes. Enzymes, complexes of amino acids united in a polypeptide chain, can be seen as specialists which demonstrate high chemo-, regio- or stereoselectivity. A number of these catalysts are applied in commercial chemical processes or are an essential part of a performance product, *e.g.* lipases (a family within the enzymes) in washing powder.

More modified or dedicated enzymes are nowadays accessible to the organic chemists. Novozym 435 is a widespread lipase (*Candida antarctica* lipase B) immobilized on an acrylic resin. Novozym 435 catalyzes esterifications, transesterifications and reactions based on aminolysis (Scheme 2.1).
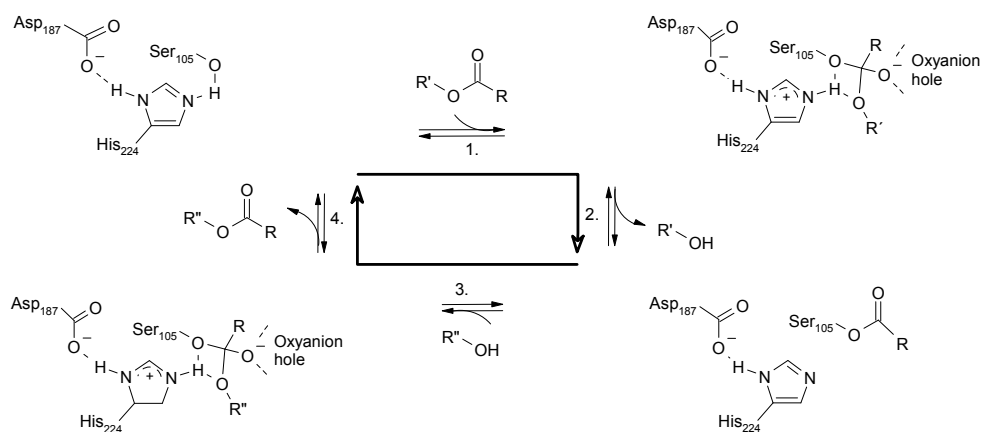


**Scheme 2.1**    *Global reaction mechanism of a transesterification by Novozym 435; (1) RR'-ester enters active site, (2) R'-alcohol leaves and enzyme is acylated, (3) R"-alcohol enters acylated active site, (4) RR"-ester leaves and active site is unoccupied.*[2]

The implementation of a biocatalyst in a synthetic route improves the accessibility of chiral intermediates or pharmaceutically active compounds.

Synergistic effects of microwave heating and biocatalysis were claimed in literature.[3,4] Rate enhancements up to a factor of 140 were reported in several cases and in general the combination of microwave heating and biocatalysis seems to work better than conventional heating. A review from Besson *et al.* gives a good picture of the current claims.[5] Reproduction of some specific examples was the first step involving biocatalysis as a mediator for kinetic resolution. A follow-up with dynamic kinetic resolution (DKR) should have been a logical next approach.[6] The DKR concept is a smart tool for realizing 100 % yield and 100 % enantiomeric purity in the production of fine chemicals and this concept will be elaborated in section 3.1.

Combinations of alcohols and esters as well as combinations of alcohols and carboxylic acids have been made to perform (enantioselective) transesterifications and esterifications with various types of enzymes. First the (enantioselective) transesterification is discussed in the next paragraph.

### Transesterification

In the classical transesterification three substitution locations at the substrates (R, R′and R″) are available to introduce a wide diversity of (by)products (Scheme 2.2 (top)). This diversity makes the transesterification an attractive reaction in a multi-step synthesis. A common substrate for the study of kinetic resolutions is 1-phenylethanol from which esters can be made (see Scheme 2.2 (bottom), Table 2.2 or Figures 2.2 - 2.10). Especially the formed alcohol enables the design of an irreversible process.
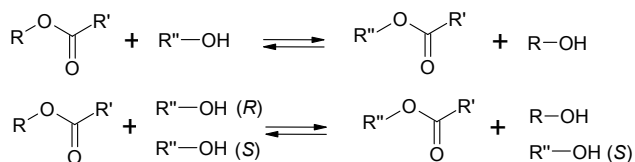


**Scheme 2.2**    *Transesterification of an ester with an alcohol (top) in general and (bottom) as an enantiomerically selective reaction.*

A combination of esters and substrate alcohols has been tested using Novozym 435 as biocatalyst (entries 1 to 6 in Table 2.2). The combinations in entries 1 and 2 have been reported by Loupy and Petit.[7] However, the procedure of Loupy and Petit[7] proved to be irreproducible and thermally uncontrollable. In their setup the biocatalyst was used as a solid carrier for the substrates by impregnation via an ethereal solution. The amount of catalyst they used was reconsidered and a more

practical and scalable quantity was applied in our work. These authors have also reported the use of isopropenyl acetate as an ester (entry 5), but instead of biocatalyst Novozym 435 they used another lipase.

The combination in entry 10 has been reported by Lin and Lin using another lipase type than Novozym 435.[8,9] Porcine pancreas lipase (PPL) is commercially available, albeit with a low activity and not stabilized. The reactivity was also tested with 1-phenylethanol, see entry 9.

From the group of Park it was known that subtilisin has an opposite enantio-selectivity compared to Novozym 435 and PPL.[10] A small amount of subtilisin was obtained from CLEA Technologies.[11] Cross-linkage of enzymes by aggregation (CLEA) also stabilizes the enzymes with preservation of most of the enzymatic activity. Although Park's coworkers did not perform the reaction with microwave heating, microwave as well as conventional heating were applied in our work (entry 7). The same combination of esters and alcohols has been tested with subtilisin (entry 8) and with Novozym 435 (entry 4).

**Table 2.2** *Biocatalytic enantioselective transesterification of (R,S)-1-phenylethanol (A) and (R,S)-1,2,3,4-tetrahydro-1-naphthol (B) with various esters by microwave heating.*

| entry | type of biocatalyst* | alcohol (R,S) | ester | conv. (%) | time (min) | ee (%) |
|---|---|---|---|---|---|---|
| 1 | Novozym-435 | A | ethyl caprylate | 42 | 10 | >99 |
| 2 | | A | ethyl caprylate | 38 ** | 10 | >99 |
| 3 | | A | vinyl acetate | 47 | 60 | >99 |
| 4 | | A | trifluoroethyl butyrate*** | 18 | 10 | >99 |
| 5 | | A | isopropenyl acetate | 48 | 60 | >99 |
| 6 | | B | isopropenyl acetate | 43 | 60 | 99 |
| 7 | Subtilisin | A | trifluoroethyl butyrate*** | 39 | 2602 | 82 |
| 8 | | A | vinyl acetate | 4.4 | 2748 | 59 |
| 9 | PPL | A | vinyl acetate | 6.4 | 1376 | 98 |
| 10 | | B | vinyl acetate | 10 | 375 | >99 |

\*    Biocatalyst:   Novozym 435 = *Candida Antartica* lipase B, immobilized on resin;
      Subtilisin = *Novozyme Alcalase*, a cross-linked aggregate[9];
      PPL = *Porcine Pancreas* lipase, free enzyme.

\*\*    Conventional heating

\*\*\*    2,2,2-Trifluoroethyl butyrate

**Figure 2.2**    *Transesterification of vinyl acetate with (R,S)-1-phenylethanol by Novozym 435 in toluene at 70 °C (left) in oil bath or (right) by microwave heating; (R)-1-phenylethyl acetate (—■—); (S)-1-phenylethyl acetate (—□—); (R)-1-phenylethanol (—•—) and (S)-1-phenylethanol (—○—), see Table 2.2, entry 3.*
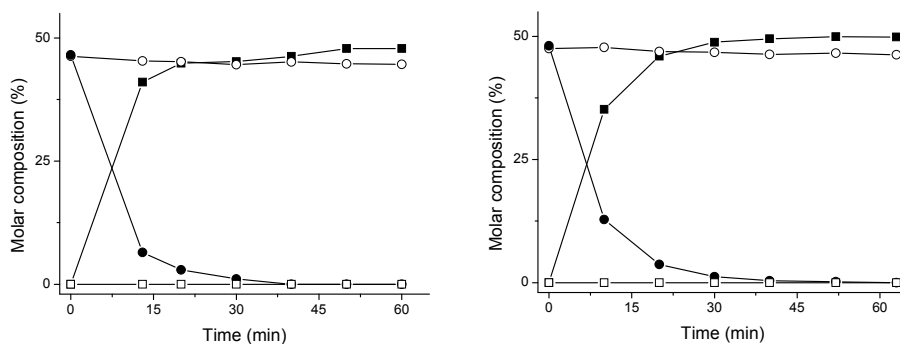


**Figure 2.3**    *Transesterification of isopropenyl acetate with (R,S)-1-phenylethanol by Novozym 435 in toluene at 70 °C in (left) oil bath or (right) by microwave heating; (R)-1-phenylethyl acetate (—■—); (S)-1- phenylethyl acetate (—□—); (R)-1-phenylethanol (—•—) and (S)-1-phenylethanol (—○—), see Table 2.2, entry 5.*
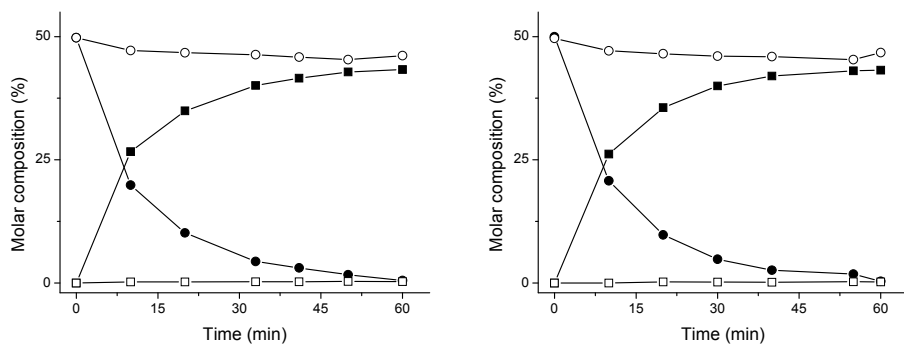
**Figure 2.4**    *Transesterification of isopropenyl acetate with (R,S)-1,2,3,4-tetrahydro-1-naphthol by Novozym 435 in toluene at 70 °C in (left) oil bath or (right) by microwave heating; (R)-1,2,3,4-tetrahydro-1-naphthyl acetate (—■—); (S)-1,2,3,4-tetrahydro-1-naphthyl acetate (—□—); (R)-1,2,3,4-tetrahydro-1-naphthol (—●—) and (S)-1,2,3,4-tetrahydro-naphthol (—○—), see Table 2.2, entry 6.*
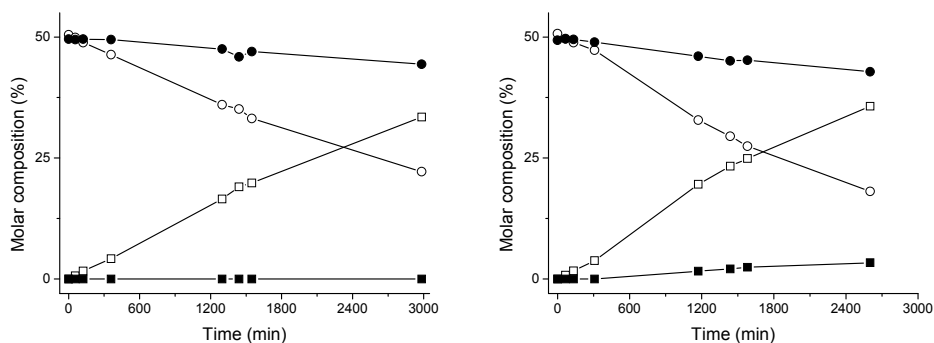


**Figure 2.5**    *Transesterification of 2,2,2-trifluoroethyl butyrate with (R,S)-1-phenylethanol by Subtilisin in THF at 40 °C in (left) oil bath or (right) by microwave heating; (R)-1-phenylethyl butyrate (—■—); (S)-1-phenylethyl butyrate (—□—); (R)-1-phenylethanol (—●—) and (S)-1-phenylethanol (—○—), see Table 2.2, entry 7.*
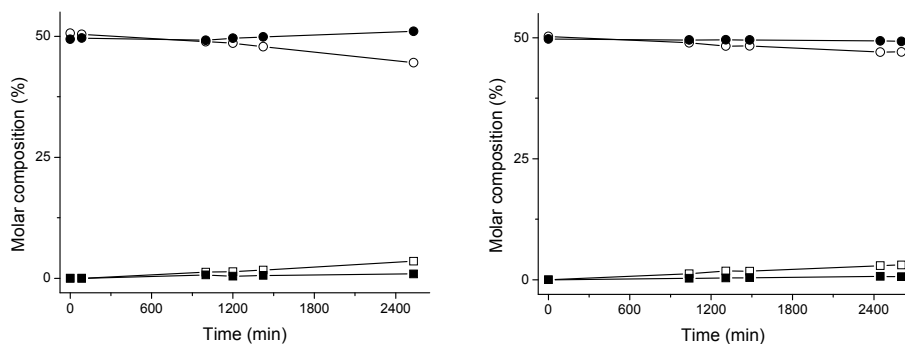
**Figure 2.6**   *Transesterification of vinyl acetate with (R,S)-1-phenylethanol by Subtilisin in THF at 40 °C in (left) oil bath or (right) by microwave heating; (R)-1-phenylethyl acetate (—■—); (S)-1-phenylethyl acetate (—□—); (R)-1-phenylethanol (—●—) and (S)-1-phenylethanol (—○—), see Table 2.2, entry 8.*



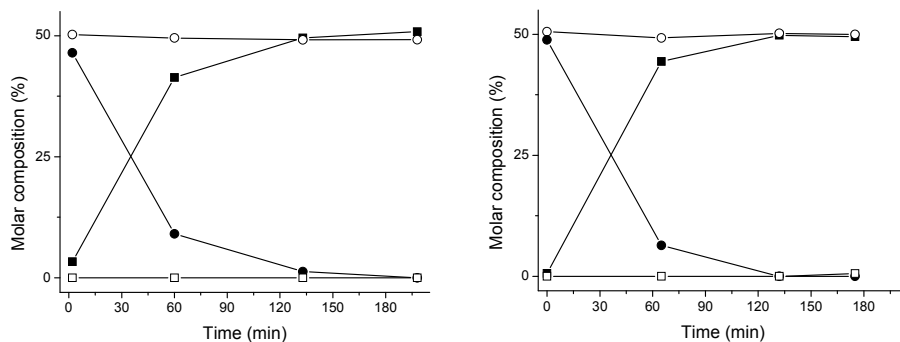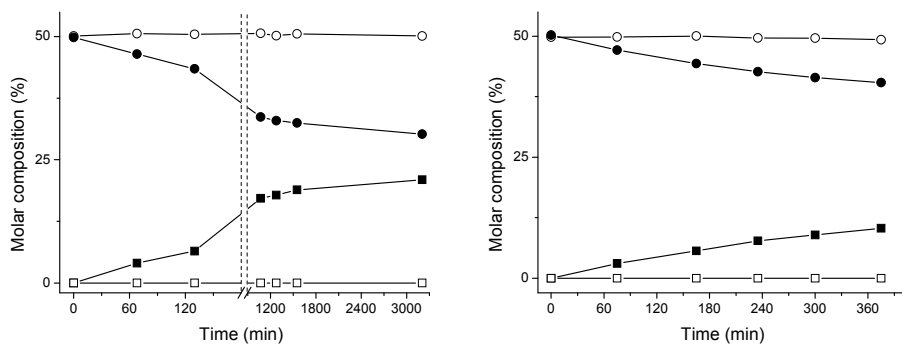**Figure 2.7**   *Transesterification of vinyl acetate with (R,S)-1-phenylethanol by PPL in toluene at 40 °C in (a) oil bath or (right) by microwave heating; (R)-1-phenylethyl acetate (—■—); (S)-1-phenylethyl acetate (—□—); (R)-1-phenylethanol (—●—) and (S)-1-phenylethanol (—○—), see Table 2.2, entry 9.*

23
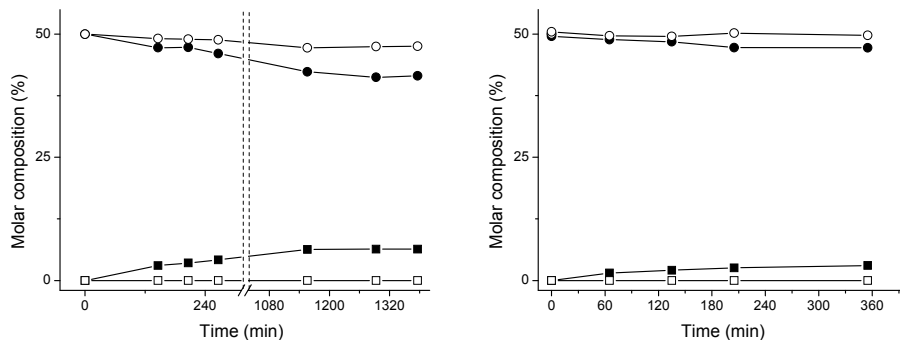
**Figure 2.8** *Transesterification of vinyl acetate with (R,S)-1,2,3,4-tetrahydro-1-naphthol by PPL in benzene at 40 °C in (left) oil bath or (right) by microwave heating; (R)-1,2,3,4-tetrahydro-1-naphthyl acetate (—■—); (S)-1,2,3,4-tetrahydro-1-naphthyl acetate (—□—); (R)-1,2,3,4-tetrahydro-1-naphthol (—•—) and (S)-1,2,3,4-tetrahydro-1-naphthol (—○—), see Table 2.2, entry 10.*

**Esterification**

Besides enantioselective transesterifications also biocatalytic esterifications have been claimed to undergo a positive microwave effect. Consequently, to verify these microwave effects the work of Yadav and Lathi has been reproduced in two cases,[3,4] namely *n*-octanol and *n*-butanol in combination with adipic acid (see Scheme 2.3, Table 2.3 and Figure 2.9). *n*-Octanol should have an initial rate enhancement factor of over 2.2. The presence of a double carboxylic acid functionality allowed to study selectivity for mono- or double-esterification for both heating methods. However, only mono-esterification was observed. Other studies on esterifications using lipozyme RM IM (LRI) claiming accelerating effects for microwave heating have been reported by Yadav *et al*.[12]



R-OH = *n*-butanol or *n*-octanol
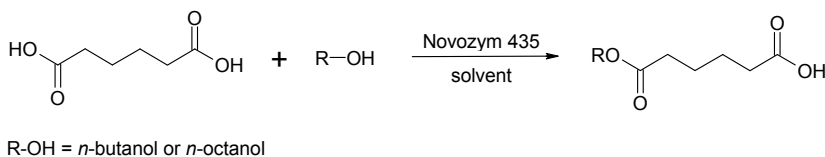
**Scheme 2.3** *Mono-esterification of adipic acid with the aid of Novozym 435.*

**Table 2.3**    *Biocatalytic esterification of adipic acid at 60 °C (conventional heating).*

| entry | type of biocatalyst* | alcohol | acid | conversion (%) | time (min) |
|---|---|---|---|---|---|
| 1 | Novozym 435 | *n*-octanol | adipic acid | 73 | 180 |
| 2 | | *n*-butanol | adipic acid | 68 | 180 |

*\* Biocatalyst: Novozym 435 = Candida Antartica lipase B immobilized on resin*
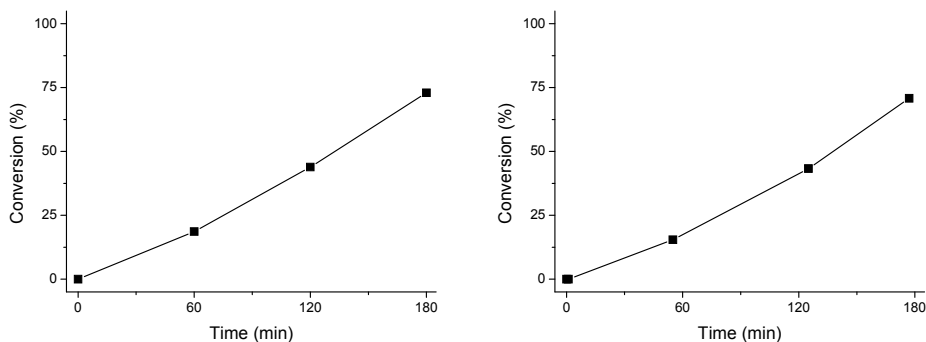


**Figure 2.9**    *Esterification of adipic acid with n-octanol by Novozym 435 in 1,4-dioxane at 60 °C (left) by conventional heating or (right) by microwave heating; n-octyl ester (—■—), see Table 2.3, entry 1.*

Besides enhanced reaction rates, an improvement in enzyme stability by microwave irradiation was claimed by the group of Besson.[13] The enzyme stability has been elaborated only briefly. The enzyme activity has been quantified by the degree of conversion after a preset period of 3 h (see Table 2.4), but has also been monitored during this period (Figure 2.10).

**Table 2.4**    *Effect of catalyst re-use (4 times) for transesterification of vinyl acetate with (R,S)-1-phenylethanol catalyzed by Novozym 435 at 70 °C in toluene; (a) conventional and (b) microwave heating.*

| entry | run | conversion (%) | | total-time (min) |
|---|---|---|---|---|
| | | (a) | (b) | |
| 1 | 1 | 51 | 49 | 180 |
| 2 | 2 | 49 | 50 | 360 |
| 3 | 3 | 46 | 47 | 540 |
| 4 | 4 | 41 | 41 | 720 |
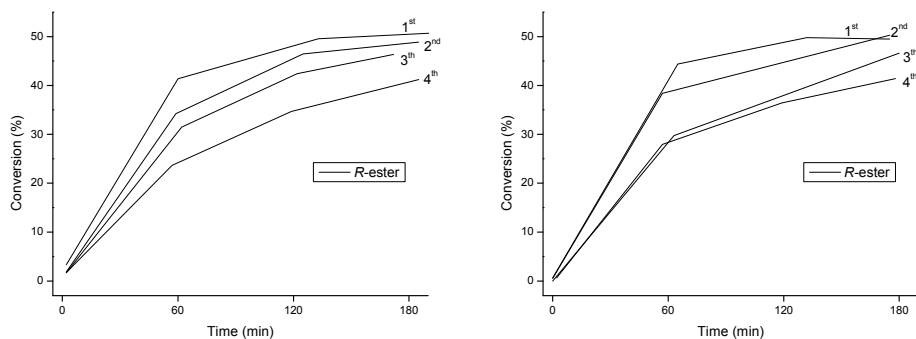
**Figure 2.10** *Activity of Novozym 435 after 4 cycles of re-usage in the trans-esterification of vinyl acetate with (R,S)-1-phenylethanol in toluene at 70 °C (left) by conventional heating and (right) by microwave heating; the conversions into (R)-1-phenylethyl acetate have been plotted against time.*

## Conclusions on the biocatalyzed (trans)esterifications

Surprisingly, in contrast to all literature referring to rate enhancements of enzymatic reactions no significant beneficial effects have been observed for each (trans)esterification carried out with microwave heating in our laboratory. All reactions show under consistent conditions a close or identical time-conversion history for conventional and microwave heating. Even a switch to a mono or single-mode microwave oven did not change the time-conversion history as compared to multi-mode heating conditions. Possible explanations for the observed effects in literature are related to the absence of proper comparison or to incorrect temperature measurements. For example, higher heating rates can be achieved by microwave heating resulting in an apparently higher conversion rates. Proper stirring and accurate internal temperature measurements form the basis of reliably comparing different heating methods. This statement is elaborated in chapter 4.

The purport of this conclusion is like peddling upstream on a fast streaming river of all reported positive claims with microwave heating in the field of biocatalysis.

## 2.4 Piperidine and piperazine formation

### Cyclization of aniline with 1,5-dibromopentane

*N*-Heterocycles are important building blocks for active pharmaceuticals. The synthesis of an *N*-aryl heterocycle like phenylpiperidine can be performed with a high atom efficiency in an aqueous medium (Scheme 2.4). The cyclization rate of

aniline-derivates in general has been reported to be enhanced by microwave heating, see the papers of the groups of Varma[14] and Collins.[15] The work-up procedure is as simple as the separation of two liquid phases as demonstrated by Varma.[14] Both starting materials (aniline and 1,5-dibromopentane) are miscible liquids in the organic layer. All reactants absorb microwave energy due to similar loss tangents, see Table 2.5. The aqueous layer contains a salt which strongly improves the absorption of microwaves.

**Table 2.5**    *Loss tangent of the components in piperidine formation.*

|  | water [a] | aniline | 1,5-dibromopentane |
|---|---|---|---|
| $\varepsilon''$ (dielectric loss) | 7.5 (298 K) | 0.56[b] | 1.5/2.11[c] |
| $\varepsilon'$ (dielectric constant) | 78 (298 K) | 7.1 (293 K)[d] | 9.1 (303 K)[d] |
| loss tangent ($\varepsilon''/\varepsilon'$) | 0.10 - 0.14 | ~0.1 | ~0.2 |

*a: [reference 16]; b: dielectric loss of 2,4-dimethylaniline at 3 GHz, 293 K [reference 17]; c: dielectric loss of 1,5-dibromopentane at 3.87 GHz, 293 K and dielectric loss of 1,4-dibromopentane in benzene at 10 GHz, 293 K, respectively [reference 18]; d: [reference 19]*

If selective heating occurs under the studied conditions, it is unlikely that the reactivity between the starting materials is thermally improved. Regardless of the method of heating, proper mixing is demanded and high mass transfer rates will also stimulate heat transport. The heat exchange is then efficient and consequently no local heating effects of any significant influence are expected.
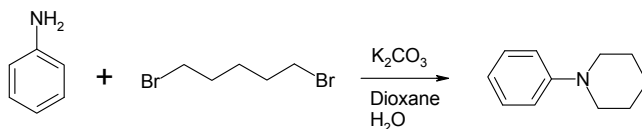


**Scheme 2.4**    *Cyclization of aniline with 1,5-dibromopentane.*

The reaction in a pure aqueous medium gave irreproducible results when test tubes under magnetic stirring were used. With a pitched-blade impeller a proper aniline/1,5-dibromopentane dispersion in water was obtained resulting in a smooth increase of the amount of product. However, separation of the aqueous and the organic phase was much more difficult for the mechanically stirred dispersions than for the magnetically stirred mixtures. The addition of an organic solvent led to better phase separation without drastic changes in the overall reaction time. The time-conversion histories of the starting materials, aniline and 1,5-dibromopentane, depicted for conventional and microwave heating in Figure 2.11.
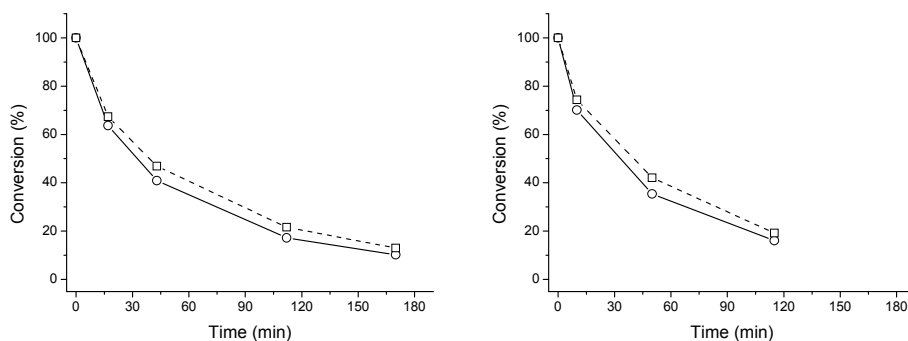
**Figure 2.11**   *Cyclization of aniline with 1,5-dibromopentane (1 eq) in H₂O/1,4-dioxane at 90 °C (left) by conventional heating and (right) by microwave heating; aniline (—□—) and 1,5-dibromopentane (—○—).*

Besides aniline also cyclohexylamine and 3-bromoaniline have been tested under reflux conditions. Cyclohexylamine and 3-bromoaniline were heated with 1,5-dibromopentane in an aqueous solution to compare conventional and microwave heating. Time-conversion histories were not significantly different for conventional and microwave heating. Table 2.6 shows the product yields after 20 minutes reaction time based on aliphatic or aromatic amine consumption.

**Table 2.6**   *Cyclization of cyclohexylamine and 4-bromoaniline with 1,5-dibromopentane*

| | yield (%)* | |
|---|---|---|
| | conventional heating | microwave heating |
| cyclohexylamine | 67 | 66 |
| 4-bromoaniline | 38 | 31 |

\*   *yield at 20 min.*

### Cyclization of 3-chloroaniline with bis-(2-chloroethyl)amine.HCl

The cyclization of 3-chloroaniline with bis-(2-chloroethyl)amine.HCl to a piperazine is a key step in the synthesis of two types of anti-depressant (Etoperidone[20] and Nefazodone[21]), see scheme 2.5.
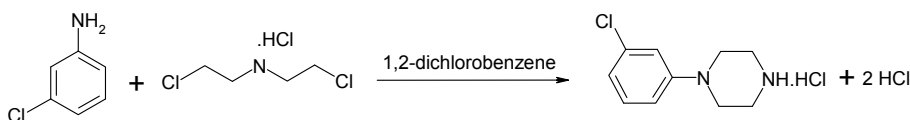


**Scheme 2.5**   *Cyclization of 3-chloroaniline with bis-(2-chloroethyl)amine.HCl.*

At first glance this cyclization looks similar to the cyclization of aniline with 1,5-dibromopentane. However, the mechanism is different through the anchimeric assistance of nitrogen giving a three-membered ring (aziridine) as intermediate species. Also the driving force of this reaction is different due to the thermal removal of hydrogen chloride gas under reflux conditions at elevated temperatures making this a (heterogeneous) gas-liquid system. Highly boiling, inert 1,2-dichlorobenzene was selected as solvent. The reactions are monitored by measuring the amount of hydrogen chloride (by titration at a constant pH) evolved from the reaction mixture at various time intervals, see Figure 2.12.
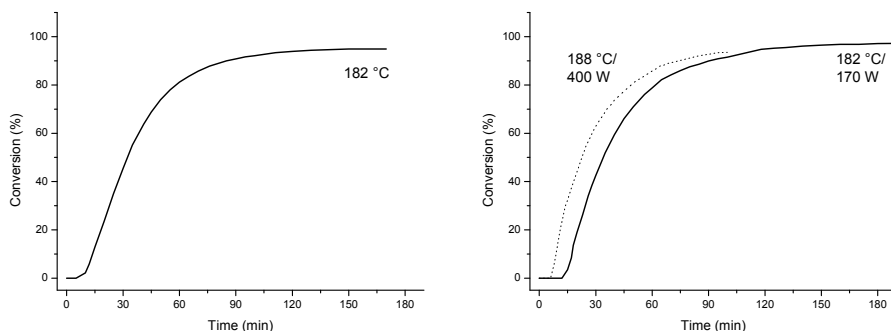


**Figure 2.12**    *Cyclization of 3-chloroaniline with bis-(2-chloroethyl)amine.HCl in 1,2-dichlorobenzene under reflux (left) by conventional heating and (right) by microwave heating.*

The absence of a microwave effect is ascertained by a fair comparison between the energy inputs of conventional and microwave heating. At 400 W‡ power input the reflux temperature was 188 °C, 6 °C higher than for 170 W‡ power input. As a consequence the conversion rate is somewhat higher at 400 W‡ than at 170 W‡ power input, resulting from a higher solubility of the reactants and a higher reaction temperature. Again for this case proper temperature control is decisive in finding the cause of any acceleration.

**Conclusions of the piperidine and piperazine formation**
The presented reactions serve as examples for liquid-liquid and gas-liquid combinations. Although these reactions cannot be standardized for the whole field of microwave-mediated organic synthesis, specific microwave effects were found to be absent.

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‡  *170 W was the average power to maintain the temperature at 182 °C. 400 W was the constant power resulting in a temperature of 188 °C.*

Under these reliable conditions the reactions are not accelerated *e.g.* by selective heating of the microwave energy. Comparison of the piperazine formation under both heating conditions is not precedented in literature.

An earlier report by Varma[18] describes a series of efficient and simple microwave-assisted syntheses of substituted piperidines in heterogeneous liquid-liquid systems. Only one example, the reaction between ethyl 4-aminobenzoate and 1,4-dibromobutane, was investigated under conventional *and* microwave heating conditions to demonstrate a specific microwave effect. Since the microwave-assisted experiment was performed in a CEM mono-mode device with a built-in infrared temperature sensor it is highly questionable whether the claimed microwave effect will hold, due to the absence of correct temperature registration.

## 2.5 Oxidation of benzyl alcohol to benzaldehyde

The oxidation of benzyl alcohol with iron(III)nitrate nonahydrate has been amply reported. Good selectivity under mild reaction conditions and convenient isolation of the products were achieved employing various inorganic supports, such as silica gel,[23] K10-clay,[24] HZSM-5 zeolite,[25-27] kieselguhr[28] and graphite.[29] The K10-clay-supported version gave reaction rate enhancements under microwave irradiation conditions in the absence of solvents.[30] The oxidation rate of benzyl alcohol has been reported to be positively influenced by a combination of microwave heating and microreactor technology (Scheme 2.6). To our surprise these rate enhancements were found for a homogeneous system when the alcohol is saturated with oxidant ($Fe(NO_3)_3.9H_2O$) in a 16 : 1 ratio.[31]
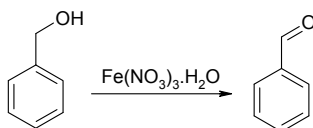


**Scheme 2.6**    *Oxidation of benzyl alcohol with iron(III)nitrate nonahydrate.*

The paper prompted us to gain more insight in the claimed microwave effect in this particular case. We investigated in detail whether microwave heating really outperforms conventional heating procedures in a batchwisely heated setup with accurate temperature control aimed at assessing the process scalability of this oxidation step.

**Results of conventional heating**

In contrast to the reactions in a flow-reactor described by Jachuck *et al*[32], the oxidation of benzyl alcohol with $Fe(NO_3)_3.9H_2O$ has been performed under aerobic conditions in an open vessel at various elevated temperatures reached by conventional heating.

<u>**Overview of operational sequence of reactions**</u>.

Our study quickly revealed that the oxidation of benzyl alcohol with $Fe(NO_3)_3.9H_2O$ includes a series of redox reactions. These reactions may occur with the oxidant and benzyl alcohol in the presence of water liberated from the nonahydrate. This water is released upon dissolution of the iron(III) salt in benzyl alcohol. The rather complex reaction network may give rise to uncertainty in the exact stoichiometry. In general this oxidation is based on the hydrolysis of iron(III)nitrate,[33] see Scheme 2.7.

$$2\,Fe(NO_3)_3 + 3\,H_2O \rightleftharpoons Fe_2O_3 + 6\,HNO_3$$
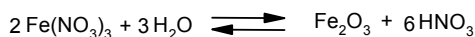
**Scheme 2.7**     *The oxidation is based on the hydrolysis of iron(III)nitrate.*

However, during the reaction also brown fumes were observed referring to the presence of $NO_2$. This phenomenon was not observed when the reaction was performed in an argon or nitrogen atmosphere, indicating a direct oxidation of NO to $NO_2$ under aerobic conditions. The absence or presence of oxygen has a profound effect on the stoichiometry of the reaction.

It was expected that iron(III) either acts as a catalyst for the oxidation under aerobic conditions or is consumed by the oxidation. Therefore, the amount of iron(III) was determined by a titration with EDTA before and after the reaction.[34] After the reaction was completed the amount of iron(III) in the reaction mixture was found to be unchanged within experimental error. However, *in situ* autodecomposition of iron(II)nitrate prevents the identification of iron(II) as a result of a redox reaction (see Scheme 2.8).[35]

$$18\,Fe(NO_3)_2 + 15\,H_2O \rightleftharpoons 4\,Fe_2O_3 + 10\,Fe(NO_3)_3 + 6\,NO + 15\,H_2O$$
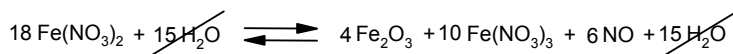
**Scheme 2.8**     *(Auto)decomposition of iron(II)nitrate reproduces iron(III).*

The role of iron(III) in the oxidation of benzyl alcohol is purely catalytic by coordinating the oxidant to the alcohol. Even though nitrate and iron(III) are combined in one salt, a molar ratio of benzyl alcohol and $Fe(NO_3)_3.9H_2O$ of 100:1 at

50 °C is insufficient to bring the reaction to completion. The conversion completely flattens out after a few hours, see Figure 2.13.

Although overall iron(III) remains in its original oxidative state, the counter-ion in its original salt form has changed into the oxide thus lowering the iron(III) concentration in solution by precipitation during the reaction.

### Formation of (by-)products.

Throughout the reaction at various temperatures the formation of two byproducts has been observed, namely benzyl nitrite[36] and benzyl nitrate.[37] The proposed sequence of reactions during the oxidation of benzyl alcohol to benzaldehyde is depicted in Schemes 2.9 and 2.10.

In Scheme 2.9 the postulated reactions lead to a 2:1 molar ratio of benzyl alcohol and $Fe(NO_3)_3.9H_2O$. To rationalize the observation that a 4:1 molar ratio nearly leads to completion, the reactions as proposed in Scheme 2.10 should also be integrated. Water and oxygen act as oxidants in this process by reactivating NO.
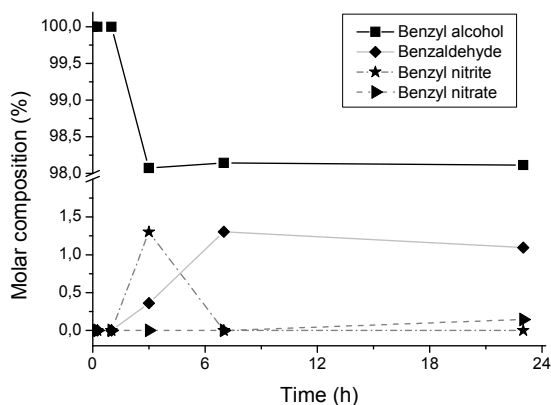


**Figure 2.13**    *Time - molar composition plot of the oxidation of benzyl alcohol at a molar ratio of benzyl alcohol and Fe(NO₃)₃.9H₂O of 100:1 at 50 °C under conventional heating and aerobic conditions.*
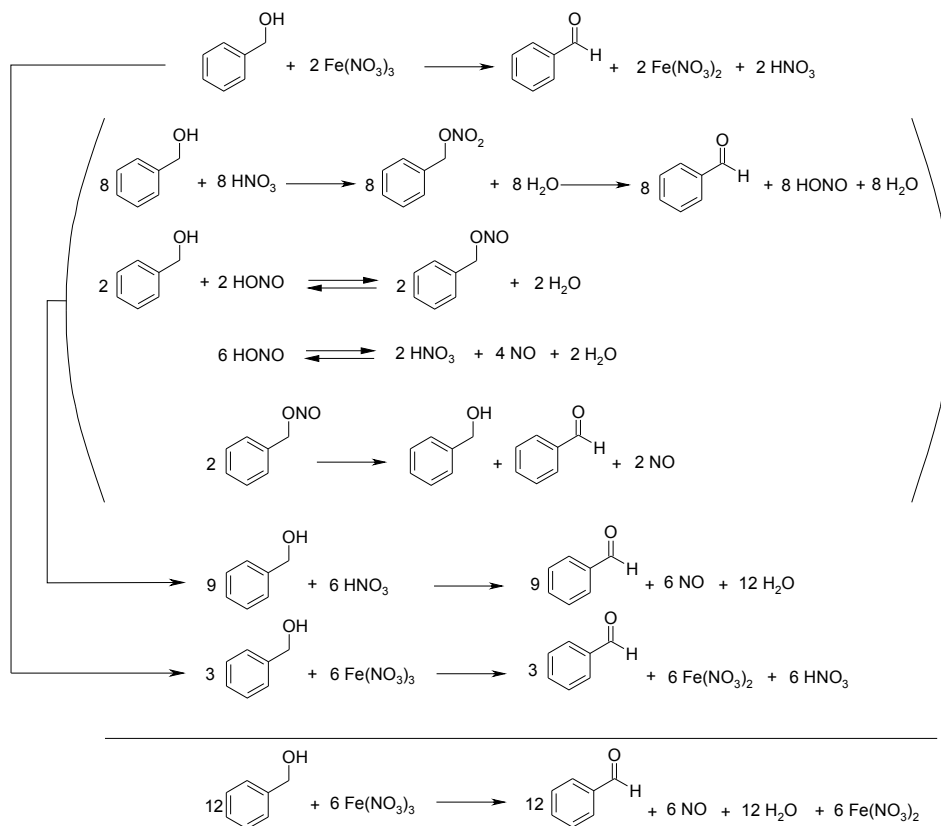
**Scheme 2.9**    *Reactions rationalizing a 2:1 ratio in stoichiometry of benzyl alcohol and Fe(NO₃)₃.9H₂O. Decomposition of iron(II)nitrate reproduces iron(III).*

$$12\ NO\ +\ 6\ O_2\ \longrightarrow\ 12\ NO_2$$
$$12\ NO\ +\ 12\ NO_2\ +\ 12\ H_2O\ \longrightarrow\ 24\ HONO$$
$$24\ HONO\ \longrightarrow\ 8\ HNO_3\ +\ 16\ NO\ +\ 8\ H_2O$$
$$\overline{\hspace{6cm}}$$
$$12\ NO\ +\ 6\ O_2\ +\ 12\ H_2O\ \longrightarrow\ 8\ HNO_3$$
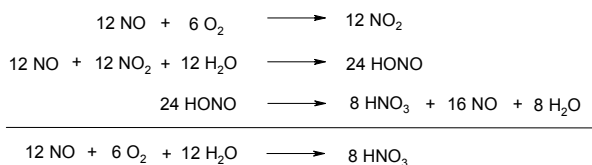
**Scheme 2.10**    *Reactions rationalizing a higher than 2:1 ratio in stoichiometry of benzyl alcohol and Fe(NO₃)₃.9H₂O.*

33

**Molar ratio benzyl alcohol and Fe(NO$_3$)$_3$.9H$_2$O**.

An increase in the amount of iron(III)nitrate, with respect to benzyl alcohol, leads to an increase of the reaction rate, see Figure 2.14 for the time-molar composition histories.
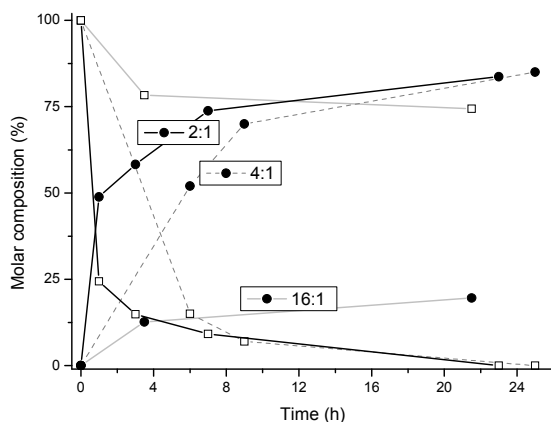


**Figure 2.14**    *Molar composition of benzyl alcohol (□) and of benzaldehyde (●) as function of the initial molar ratio of benzyl alcohol and oxidant at 50 °C under conventional heating and aerobic conditions.*

At a molar ratio of 16:1 (benzyl alcohol : Fe(NO$_3$)$_3$.9H$_2$O) at room temperature benzyl alcohol was found to be saturated with Fe(NO$_3$)$_3$.9H$_2$O affording a homogeneous solution. Larger amounts of Fe(NO$_3$)$_3$.9H$_2$O resulted in two liquid phases. In those cases the bottom layer primarily consists of inorganic salt, melting point 47 °C, while the top layer is rich in benzyl alcohol. The heterogeneous nature of such reaction systems hampers a simple kinetic evaluation of the oxidation process. Each reaction mixture with varying amounts of Fe(NO$_3$)$_3$.9H$_2$O eventually forms a substantial amount of red-brown sediment on the reactor wall. An XPS analysis of the sediment points to a mixture of Fe(NO$_x$)$_y$. The formation of sediment is explained in Schemes 2.7 and 2.8. Nearly full conversion within one hour was achieved at 100 °C when a 4:1 molar ratio of benzyl alcohol and Fe(NO$_3$)$_3$.9H$_2$O was applied giving a selectivity of 75 % to benzaldehyde, see Figure 2.15. Two important issues are noteworthy. Firstly, overoxidation leading to benzoic acid has been observed in all cases, which implicates the presence of an optimum for the conversion to benzaldehyde. Secondly, high temperatures should be avoided due to instability of the byproducts during this oxidation step.[38]

**Results of microwave heating**

In a next step, the influence of microwave heating on the course of the oxidation of benzyl alcohol was assessed at temperatures of 50 °C and 100 °C. These two temperature levels were primarily used to gain insight into the potential of microwave heating (MW) compared to conventional heating (CH) as claimed by Jachuck *et al.*[27] The molar compositions of benzaldehyde and benzyl alcohol in the reaction mixture are shown in Figure 2.15.
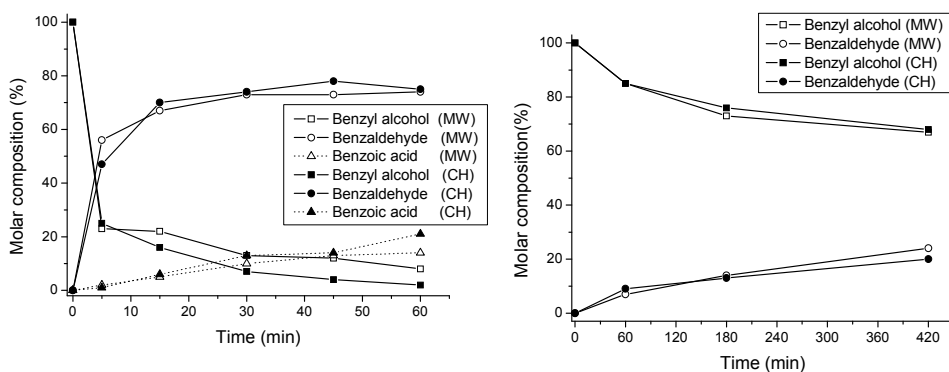


**Figure 2.15**       *(left) Time - molar composition plot of the oxidation of benzyl alcohol at a ratio of benzyl alcohol and oxidant of 4:1 at 100 °C under comparable conventional (CH) and microwave (MW) heating; aerobic conditions. (right) Time - molar composition plot of the oxidation of benzyl alcohol at a ratio of benzyl alcohol and oxidant of 16:1 at 50 °C under comparable conventional (CH) and microwave (MW) heating; aerobic conditions.*

Experiments with conventional and microwave heating at 50 °C and 100 °C can be directly compared due to similar reaction vessels, stirring speeds and heating profiles. Surprisingly, significantly higher reaction rates with microwave heating were not observed at 100 °C for the selected experimental conditions (4:1 molar ratio of benzyl alcohol and $Fe(NO_3)_3.9H_2O$). Subsequently, no beneficial effect was observed either for a 16:1 molar ratio of benzyl alcohol and $Fe(NO_3)_3.9H_2O$ under equal initial reaction conditions at 50 °C (Figure 2.15).

**Conclusions of the oxidation of benzyl alcohol**

In conclusion, by direct comparison (*i.e.* open vessels, same stirrer speeds, same heating rates and internal temperature measurements) of the oxidation of benzyl alcohol with iron(III)nitrate nonahydrate under atmospheric conditions for homogeneous (initially) and heterogeneous reaction mixtures did not reveal any positive microwave effect.

Based on the results obtained for both conventional and microwave heating it is concluded that a conventional batch heating procedure should be selected as the method of choice for a scalable process. This conclusion is supported by the observation that any microwave-induced reaction-rate enhancement is lacking when the heating conditions are systematically compared. Neither processing in a continuous mode nor microprocessing are preferable due to the necessity of aerobic conditions for completion of the reaction with minimal economical amounts of oxidant, the formation of a sediment during the reaction and the evolution of nitric fumes. The tremendously high heating rate as a result of a strong absorption of microwave energy by the reaction mixture leads to the conclusion that microwave heating is not the preferred method for safe operations on larger scales. These high heating rates lead to a rapid increment of temperature (and pressure) when the reaction is performed in a closed system with indirect temperature control as was probably the case in the described experiments.[26] In general accurate temperature control is a prerequisite for assignment of microwave effects based on different rate constants.

## 2.6 Williamson synthesis with gallic acid derivative

Aliphatic tails in molecules are known for their stimulation to molecular arrangement and contribution to the formation of *e.g.* micelles. A specific gallic acid derivate (see Scheme 2.11), characterized by triple long aliphatic side-chains, is used in the synthesis of macromolecules. Stacking and shielding of relative polar charges are related features in these macromolecules. One derivative (methyl 3,4,5-tri-dodecyloxybenzoate) has been used in our group for further optimization of the synthesis and for scaling-up.[39,40]
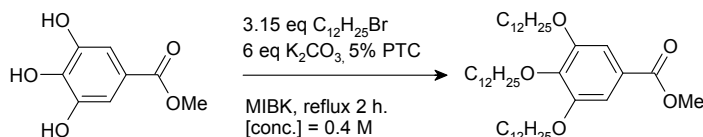


**Scheme 2.11**     *Williamson synthesis with the methyl ester of gallic acid.*

Mainly due to the heterogeneous character caused by an excess of potassium carbonate in this chemical reaction, the synthesis of methyl 3,4,5-tri-dodecyloxybenzoate was selected for investigation with microwave heating in comparison to conventional heating. The excess of base, present in six molar equivalents with respect to the methyl ester of gallic acid, demonstrated the necessity of mechanical stirring. The optimal conditions as performed in earlier

work[39] (and slightly adapted conditions, which are not further elaborated) under microwave or conventional heating resulted in similar time – conversion histories (see Figure 2.16).
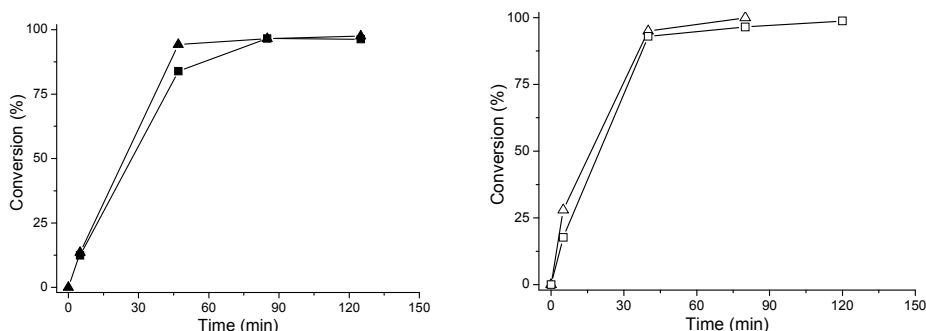


**Figure 2.16** *Williamson synthesis of methyl 3,4,5-tri-dodecyloxybenzoate (left) by conventional heating and (right) by microwave heating (duplicated runs).*

### Conclusions of the Williamson synthesis

With a large amount of a heterogeneous base in the Williamson synthesis, the overall reaction rate has not been affected by microwave heating. Clearly the rate-determining step, the conversion of the three potassium phenolate intermediates, was not significantly influenced. During this reaction, sufficient mixing and good temperature control was needed to make a fair comparison between conventional and microwave heating.

## 2.7 Laurydone process

To the best of our knowledge, production of Laurydone® is the first fine chemical process performed on large scale (1 m$^3$ reactor) with microwave heating.[41] Laurydone is used in the formulation of cosmetic products and particularly in the manufacture of lipsticks.[42,43] The reaction involves an esterification of (*S*)-pyroglutamic acid with an aliphatic alcohol (see Scheme 2.12).
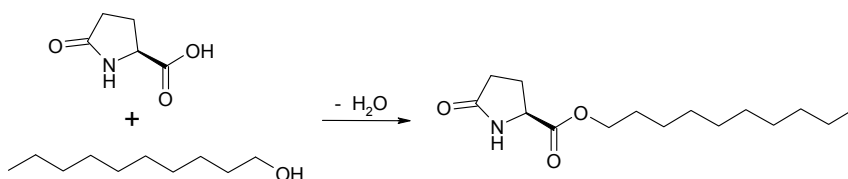


**Scheme 2.12** *Esterification of (S)-pyroglutamic acid with n-decanol.*

According to early reports this process was described as being catalyzed by *p*-toluene sulfonic acid[44] and sulfuric acid[45] in an appropriate solvent (*e.g.* toluene). After optimization addition of a solvent and a catalyst were proven to be superfluous.[44] Finally, the esterification is performed under neat conditions at elevated temperature (150 °C) by microwave heating. In this way the product is easier to purify (no acidic catalyst contamination) and no solvent removal is needed.

The final process design was a cooperation between Bioeurope, SAIREM and De Dietrich companies. The industrial realization was partially financed by the French ADEME (Agency for Environment and Energy Control). With respect to the first reports involving the synthesis of Laurydone, the process was simplified. These simplifications resulted in energy plus chemicals savings and the process time was reduced by a factor of five. The claim of reduction of the process time was based on comparing a conventionally heated process using toluene and *p*-toluenesulfonic acid at reflux temperature (110 °C) with a microwave-heated process without solvent and catalyst at 150 °C. Moreover, in the conventionally heated process a complicated work-up procedure was necessary. According to these reports it remained unclear whether a conventionally heated experiment with all the optimized parameters would reveal a microwave effect for this reaction. See chapter 5 for a picture and a description of the flow sheet (Figure 5.2).
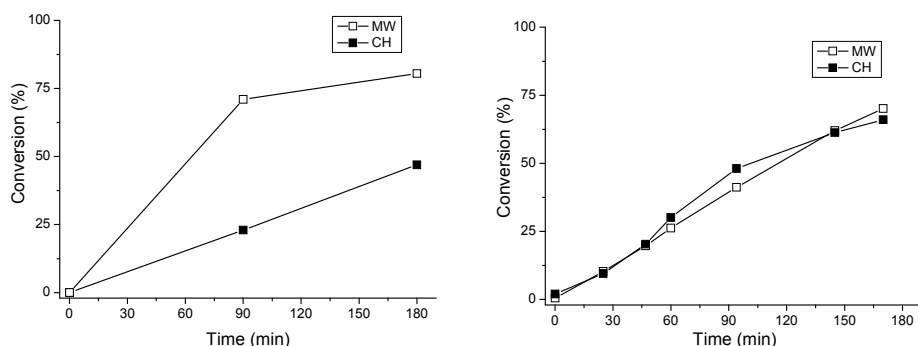


**Figure 2.17**    *Esterification of pyroglutamic acid with n-decanol; initial experiments with (left) (R,S)-pyroglutamic acid (7 mmol) at 145 °C in a test-tube with magnetic stirring and (right) (R,S)-pyroglutamic acid (97 mmol) at 145 °C in a 50 mL glass vessel with mechanical stirring (pitched-blade impeller). See also section 2.8 [experimental section] Figure 2.19 for pictures of experimental setup.*

Our experiments were aimed at reproducing the results reported by Rochas[42] and at allowing an accurate comparison between conventional and microwave heating. Initial experiments were conducted with racemic pyroglutamic acid (mp = 182-185 °C, see Figure 2.17), but later a switch was made to (S)-pyroglutamic acid (mp = 155-160 °C, see Figure 2.18). In the original recipe also (S)-pyroglutamic acid was reported. Melting points of both stereochemical forms (racemic and (S)-pyroglutamic acid) differ so strongly that the heterogeneity in the initial stages of the reaction is significantly different. Also the solubility of the enantiomerically pure pyroglutamic acid proved to be higher in n-decanol. Both factors gave rise to a higher reaction rate for (S)-pyroglutamic acid than for racemic pyroglutamic acid.
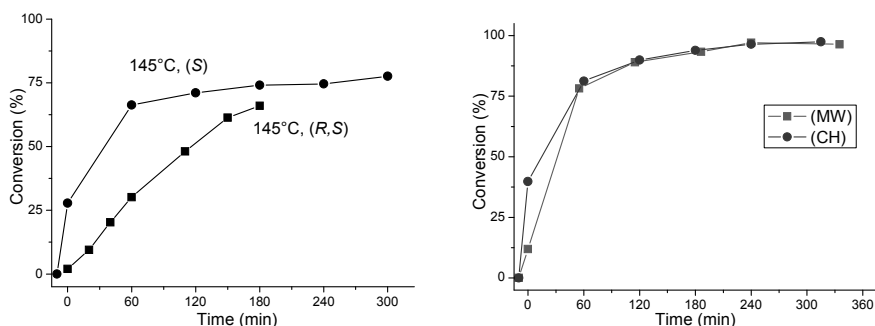


**Figure 2.18**    *Esterification of pyroglutamic acid with n-decanol; (left) (S)- and (R,S)-pyroglutamic at 145 °C in a glass vessel with overhead stirring by conventional heating and (right) (S)-pyroglutamic acid at 150 °C with an argon flow over the reaction mixture by microwave and conventional heating.*

**Conclusions of the Laurydone process**

The French-German collaboration gave an intriguing and interesting example of an industrial application of microwave heating on large scale. The handicap of the limited penetration depth of microwaves was overcome by the application of a loop system. As can be concluded from Figure 2.17 the microwave effect of a factor 3 (also reported by the French authors) in reaction rate difference between conventional and microwave heating conditions vanished when a more efficient stirring method was selected. This surprising result can be attributed to an improvement in mass-transport and more importantly to approach a more homogeneous distribution of temperature in the reaction mixture for both heating techniques, due to ideal mixing (see Figure 2.17). A precedent in the literature showed similar results.[46]

The results collected in Figures 2.17 and 2.18 demonstrate that a comparable result could have been achieved when the esterification would have been performed under conventional heating conditions at 150 °C. Although the admirable efforts demonstrate as such that microwave heating in process scaling-up is feasible, in our opinion the added value of microwave heating in comparison with conventional heating is lacking.

Also the Laurydone synthesis nicely demonstrates that small changes in solubility may have a direct effect on the reaction rate.

## 2.8 Concluding remarks

The appearance of a (real) microwave effect under microwave heating is not as trivial as it may seem from the numerous publications claiming rate enhancements. All chemical conversions investigated in this chapter can be attributed to simple thermal effects. Kappe[47] and Gedeye[48] demonstrated that in multiple cases earlier claimed microwave effects were based on inaccurate temperature measurements and ineffective stirring. Kappe[47] demonstrated that temperature differences in the reaction vials for the top, middle and the bottom sections vary up to 40 °C. Also internal temperature measurements using a fiber optic proved to be superior to register the temperature at the external wall of the vial by infrared.

Nevertheless, some cases seem to display a microwave effect even with good temperature control. Two such cases have been thoroughly investigated to reveal the cause of this observed microwave effect in chapters 3 and 4. Intriguingly, the heterogeneity of the reaction systems proved to have a profound effect.

Furthermore, a positive remark can be made regarding the experimental setup of microwave heating in a laboratory environment. The equipment is ideally suited for working under pressure in closed systems, which enhances reaction rates and allows use of low boiling solvents. Rapid heating and automation are two advantages of applying microwave heating. In most cases of microwave heating, the energy can be introduced directly and efficiently, but apolar solvents/liquids require an "accelerator" to heat up.

## 2.9 Experimental section

*General Methods; Chiral gas chromatography (GC) was performed on a Shimadzu 6C-17A GC equipped with a Chrompack Chirasil-DEX CG (DF=0.25) column and a FID. Injection temperature was set at 250 °C and the detection temperature was set at 300 °C. Temperature programs were used to optimize the analysis for each reaction mixture, see each procedure. Tetradecane was used as an internal standard.*

*The XPS (X-ray photoelectron spectroscopy) measurements were carried out with a VG Escalab MKII spectrometer, equipped with a dual Al/Mg Kα X-ray source and a hemispherical analyzer with a five-channeltron detector. Spectra were obtained using the aluminum anode (Al Kα = 1486.6eV) operating at 300 W and a constant pass energy of 20 eV with a background pressure of 2 x 10⁻⁹ mbar.*

*All microwave-heated experiments were performed in a MicroSynth of Milestone srl., Italy with internal fibre-optic (type ATC-FO; fluoroptic probe) temperature measurement via a Teflon-coated ceramic well. In general all reactions were temperature controlled with a set power maximum to obtain the thermal set-point.*
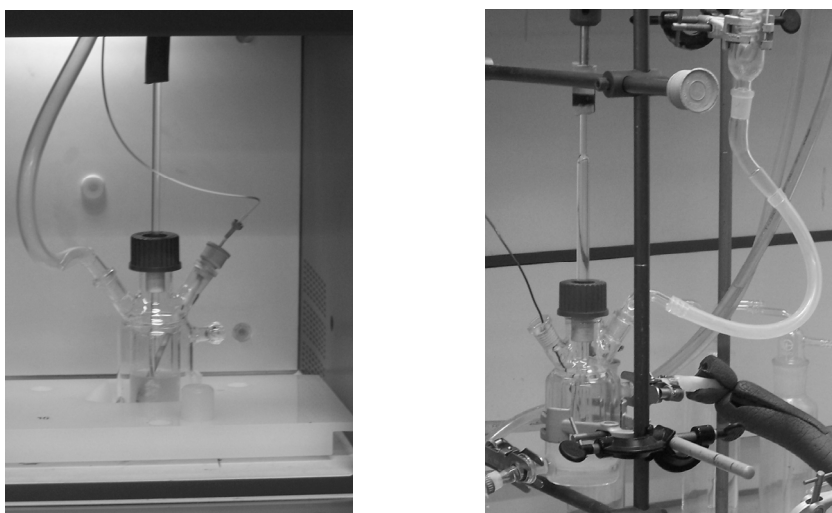


**Figure 2.19**  *A 50 mL double-walled reactor positioned in (left) the microwave cavity with mechanical stirrer (pitched-blade impeller) and fiber optic temperature sensor and (right) a similar reaction setup under conventionally heated conditions.*

**Transesterifications** *(Microwave oven; average power: ~17 W / max: 300 W)***:**

***Ethyl caprylate with (R,S)-1-phenylethanol [Table 2.1; entries 1,2];*** *A 25 mL pear-shaped flask was charged with Novozym 435 (104 mg), a solution of diethyl ether (2 mL) with (R,S)-1-phenylethanol (244 mg, 2 mmol) and ethyl caprylate (1035 mg, 6 mmol). The (magnetically stirred) reaction mixture was heated till 90 °C for a period of 10 min. After cooling the mixture was diluted with diethyl ether (10 mL) and filtered over cotton, and washed with diethyl ether. The filtrate was analyzed by GC. During reaction it was impossible to take aliquots because of absorbed liquid by the excess of catalyst.*

***Vinyl acetate with (R,S)-1-phenylethanol [Table 2.1; entry 3];*** *A 25 mL pear-shaped flask was charged with a solution of toluene (7 mL) with (R,S)-1-phenylethanol (480 mg, 4 mmol) and vinyl acetate (1722 mg, 20 mmol). The (magnetically stirred) reaction mixture was heated till 70 °C. Subsequently, Novozym 435 (50 mg) was added and the temperature was maintained for a period of 60 min. After cooling the mixture was diluted with diethyl ether and filtered over cotton, and the residue washed with diethyl ether. The combined filtrates were analyzed by GC. During reaction aliquots were taken from the liquid phase and analyzed by GC.*

***2,2,2-Trifluoro-ethyl butyrate with (R,S)-1-phenylethanol [Table 2.1; entry 4];*** *A 25 mL pear-shaped flask was charged with a solution of (R,S)-1-phenylethanol (480 mg, 4 mmol) and 2,2,2-trifluoro-ethyl butyrate (1722 mg, 20 mmol) in toluene (7 mL). The (magnetically stirred) reaction mixture was heated till 70 °C. Subsequently, Novozym 435 (50 mg) was added and the temperature was maintained for a period of 10 min. After cooling the mixture was diluted with diethyl ether and filtered over cotton, and the residue washed with diethyl ether. The combined filtrates were analyzed by GC. During reaction aliquots were taken from the liquid phase and analyzed by GC.*

***Isopropenyl acetate with (R,S)-1-phenylethanol [Table 2.1; entry 5];*** *A 25 mL pear-shaped flask was charged with a solution of (R,S)-1-phenylethanol (244 mg, 2 mmol) and isopropenyl acetate (1001 mg, 10 mmol) in toluene (5 mL). The (magnetically stirred) reaction mixture was heated till 70 °C. Subsequently, Novozym 435 (100 mg) was added and the temperature was maintained for a period of 60 min. After cooling the mixture was diluted with diethyl ether and filtered over cotton, and the residue washed with diethyl ether. The combined filtrates were analyzed by GC. During reaction aliquots were taken from the liquid phase and analyzed by GC.*

***Isopropenyl acetate with (R,S)-1,2,3,4-tetrahydro-1-naphthol [Table 2.1; entry 6];***
*A 25 mL pear-shaped flask was charged with a solution of (R,S)-1,2,3,4-tetrahydro-1-naphthol (297 mg, 2 mmol) and isopropenyl acetate (996 mg, 10 mmol) in toluene (5 mL. The reaction (magnetically stirred) mixture was heated till 70 °C. Subsequently, Novozym 435 (100 mg) was added and the temperature was maintained for a period of 60 min. After cooling the mixture was diluted with diethyl ether and filtered over cotton, and the residue washed with diethyl ether. The combined filtrates were analyzed by GC. During reaction aliquots were taken from the liquid phase and analyzed by GC.*

***2,2,2-Trifluoro-ethyl butyrate with (R,S)-1-phenylethanol [Table 2.1; entry 7];*** *A 25 mL pear-shaped flask was charged with a solution of (R,S)-1-phenylethanol (305 g, 2.5 mmol) and 2,2,2-trifluoro-ethyl butyrate (851 mg, 5.0 mmol) in THF (6.6 g). The (magnetically stirred) reaction mixture was heated till 40 °C. Subsequently, Subtilisin (50 mg) was added and the temperature was maintained for a period over 40 h. After cooling the mixture was diluted with diethyl ether and filtered over cotton, and the residue washed with diethyl ether. The combined filtrates were analyzed by GC. During reaction aliquots were taken from the liquid phase and analyzed by GC.*

***Vinyl acetate with (R,S)-1-phenylethanol [Table 2.1; entry 8];*** *A 25 mL pear-shaped flask was charged with a solution of (R,S)-1-phenylethanol (305 mg, 2.5 mmol) and vinyl acetate (430 mg, 5 mmol) in THF (6.6 g). The (magnetically stirred) reaction mixture was heated till 40 °C. Subsequently, Subtilisin (25 mg) was added and the temperature was maintained for a period over 40 h. After cooling the mixture was diluted with diethyl ether and filtered over cotton, and the residue washed with diethyl ether. The combined filtrates were analyzed by GC. During reaction aliquots were taken from the liquid phase and analyzed by GC.*

***Vinyl acetate with (R,S)-1-phenylethanol [Table 2.1; entry 9];*** *A 25 mL pear-shaped flask was charged with a solution of (R,S)-1-phenylethanol (415 mg, 3.4 mmol) and vinyl acetate (1.46 g, 16.9 mmol) in toluene (15 mL). The (magnetically stirred) reaction mixture was heated till 40 °C. Subsequently, PPL (1.0 g) was added and the temperature was maintained for a period over 6 h for microwave heating and over 40 h for conventional heating. After cooling the mixture was diluted with diethyl ether and filtered over cotton, and the residue washed with diethyl ether. The combined filtrates were analyzed by GC. During reaction aliquots were taken from the liquid phase and analyzed by GC.*

*Vinyl acetate with (R,S)-1,2,3,4-tetrahydro-1-naphthol  [Table 2.1; entry 10];* *A 25 mL pear-shaped flask was charged with a solution of benzene (3 mL) with (R,S)-1,2,3,4-tetrahydro-1-naphthol (102 mg, 0.7 mmol) and vinyl acetate (293 g, 3.5  mmol). The (magnetically stirred) reaction mixture was heated till 40 °C. Subsequently, PPL (608 mg) was added and the temperature was maintained for a period over 6 h for microwave heating and over 20 h for conventional heating. After cooling the mixture was diluted with diethyl ether and filtered over cotton, and the residue washed with diethyl ether. The combined filtrates were analyzed by GC. The filtrate was analyzed during reaction aliquots were taken from the liquid phase and analyzed by GC.*

**Esterifications:**

*Adipic acid with n-butanol or n-octanol  [Table 2.2; entries 1,2];* *A 25 mL pear-shaped flask was charged with adipic acid (1.46 g, 10 mmol) and 1 equivalent of alcohol (0.74 g of n-butanol or 1.30 g n-octanol, 10 mmol) and the total volume was adjusted with 1,4-dioxane till 20 mL. The (magnetically stirred) reaction mixture was heated till 60 °C. Subsequently, Novozym 435 (70 mg) was added and the temperature was maintained for a period over 3 h. After cooling the mixture was diluted with diethyl ether and filtered over cotton, and the residue washed with diethyl ether. The combined filtrates were analyzed by GC. During reaction aliquots were taken from the liquid phase and analyzed by GC.*

**Piperidine/piperazine formation:**

*Cyclization of aniline with 1,5-dibromopentane  [Scheme 2.4];* *A 50 mL reaction vessel equipped with an overhead stirrer (265 rpm) was charged with 1,5-dibromopentane (1281 mg, 5 mmol), aniline (463 mg, 5 mmol) and a solution of $K_2CO_3$ (760 mg, 5 mmol) in $H_2O$/1,4-dioxane (10 mL / 10 mL). The reaction mixture was heated till 90 °C, and the temperature was maintained for a period over 120 min. After cooling the mixture was allowed to separate phases with addition of ethyl acetate (10 mL). Organic phase (upper) was used for taking aliquots. The conversion of starting materials was analyzed by GC. (Microwave oven; average power: 30 W / max: 100 W)*

*Cyclization of 3-chloro-aniline with bis-(2-chloroethyl)amine.HCl [Scheme 2.5];* *A 50 mL flask was charged with 3-chloroaniline (3.68 g, 28.8 mmol) and a suspension of bis-(2-chloroethyl)amine.HCl (5.14 g, 28.8 mmol) in 1,2-dichlorobenzene (20 mL). The reaction mixture was heated to reflux (182 °C) at a set temperature of an oil bath at 200 °C during a period of 120 min (magnetically stirred). The conversion was monitored in time (intervals of 10 min.) by titrating the gaseous HCl after collection in a NaOH-solution with a constant pH of 12, with a pH-stat.*

**Oxidation of benzyl alcohol to benzaldehyde:**

*Typical procedure: Benzyl alcohol (1.0 mL, 9.7 mmol) and 1,3,5-tri-tert-butylbenzene (10 mg, 0.041 mmol) as internal standard were introduced in a 10 mL two-neck round-bottomed flask, and heated in an oil bath or microwave oven. When the mixture reached the selected temperature, $Fe(NO_3)_3.9H_2O$ (0.24 g, 0.6 mmol) was introduced, and the (magnetically stirred) reaction was started. When the desired reaction time was reached, the reaction mixture was eluted over a short silica column with a 5 µm-filter attached to the end, with an excess of diethyl ether. The diethyl ether phase was dried with $MgSO_4$, filtered, and evaporated to yield the product(s). $^1H$-NMR ($CDCl_3$, 200 MHz) typical signals δ (ppm) 4.70 (s, 2H, benzyl alcohol), 5.43 (s, 2H, benzyl nitrate), 5.71 (s, 2H, benzyl nitrite), 10.03 (s, 1H, benzaldehyde).*

*__Iron(II) determination;__ Quantatively a suitable amount of specimen was transferred into 5 ml of 4 M HCl. The content was heated to approximately 60 °C. The filter was washed with ample distilled water. The volumetric flask was filled till its final volume. A suitable amount was pipetted into a beaker and the indicator 1,10-phenanthroline (see preparation of 1,10-phenanthroline solution) was added. A Ce(IV)-solution (see preparation of Ce(IV)-solution) was titrated till color change from orange to grey.*

*__Preparation of 1,10-phenanthroline solution;__ Analytical grade 1,10-phenanthroline (49.60 mg) was added to distilled water and diluted to 250 mL.*

*__Preparation of Ce(IV)-solution (0,1 M);__ Ammonium cerium(IV) sulphate (64-66 g) was added into a solution prepared by adding concentrated sulphuric acid (28 mL) to water (500 mL): the mixture was stirred until the solid had dissolved. The content was transferred into a 1 L graduated flask, and made up to the mark with distilled water.*

*__Iron(III) determination;__ A volume of 25 mL iron(III) solution (0.1 M) was pipetted into a conical flask and diluted to 100 mL with de-ionised water. The pH was adjusted to 2-3; Congo-red paper was used – to the first perceptible color change. A number of 5 drops of the indicator solution was added, the contents of the flask was warmed to 40 °C, and titrated with standard (0.1 M) EDTA solution until the initial blue color of the solution turned grey just before the end point, and with the final drop of reagent changed to yellow.*

*__Preparation of EDTA-solution (0,1 M);__ Dry disodium dihydrogenethylenediamine tetra-acetate (37.224 g) was dissolved in distilled water and diluted to 1000 mL.*

*__Preparation of variamine blue-solution (0,1 M);__ A quantity variamine blue (1 g) was dissolved in de-ionised water (100 mL).*

**Williamson synthesis:**

***Synthesis of methyl 3,4,5-tri-dodecyloxy benzoate:*** *A 50 mL glass reactor vessel was charged with methyl gallate (0.74 g, 4 mmol), $K_2CO_3$ (3.32 g, 24 mmol), tetrabutylammonium bromide (TBAB, 65 mg, 0.2 mmol), MIBK (10 mL) and 1-bromododecane (3.09 g, 13 mmol). Subsequently, the reaction mixture was heated to reflux (120 °C) and stirred with a pitch-blade impeller at 800 rpm for 2 h. The conversion of the reaction was monitored by $^1$H-NMR. Upon completion the brown mixture was cooled to below 100 °C, and water (10 mL) was added. The aqueous layer was separated, and the organic layer was washed with water (10 mL), diluted HCl solution (10 mL 1.0 M), and water (10 mL) again. $^1$H-NMR (acetone-d6, 300 MHz): 7.27 (s, 2H, ortho-H), 4.11-3.98 (m, 6H, $OCH_2$), 3.85 (s, 3H, $OCH_3$), 1.90-1.70 (m, 6H, $OCH_2CH_2$), 1.55-1.20 (m, 4H, $(CH_2)8$), 0.86 (t, 9H, $CH_3$). (Microwave oven; average power: 50 W / max: 300 W)*

**Laurydone process:**

***Synthesis of Laurydone:*** *A 50 mL glass reactor vessel was charged with (R,S) or (S)-pyroglutamic acid (12.5 g, 97 mmol,) and n-decanol (13.75 g, 87 mmol). The reaction mixture was heated to 150 °C within 10 min and stirred with a pitch-blade impeller at 550 rpm for 3 h. Initially the reaction mixture was heterogeneous, but within a few minutes the mixture was homogeneous. During reaction aliquots were taken and analyzed by $^1$H-NMR ($CD_3OD$, 300 MHz) typical signals δ (ppm) 4.14 (t, 2H, $CH_2$-OCO, product), 3.53 (t, 2H, $CH_2$-OH, decanol). (Microwave oven; average power: 25 W / max: 400 W)*

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# Chapter 3

# 3

# Racemization of N-acetyl amino acids

# Abstract

Racemization as part of a dynamic process or classical resolution process can make the difference between 50 % and full conversion of the substrate.

The racemization of *N*-acetylindoline-2-carboxylic acid has been studied by conventional and microwave heating under various conditions. This study revealed beneficial microwave effects. The magnitude of this effect is governed by the degree of heterogeneity of the reaction system. The amount of catalyst, the temperature and amount of co-solvent played a decisive role. The microwave effect vanished when a homogeneous solution was obtained. Additionally, a significant rate enhancement was observed during microwave heating of the heterogeneous racemization mixture of *N*-acetyl-phenylalanine in *p*-xylene.

For both examples the microwave effects could be rationalized by selective heating of the boundary layer *i.e.* the interphase of solid and liquid.

Locally, the enhanced temperature increases the solubility of the substrates and consequently the rate of racemization.

3
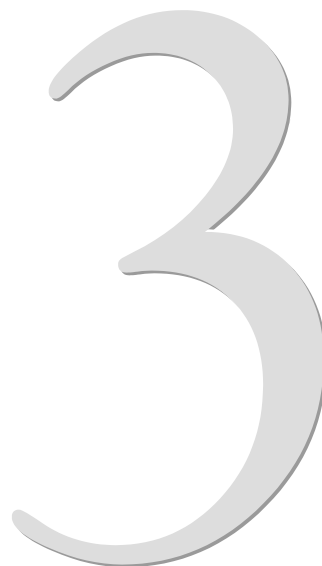
## 3.1 Introduction

Enzymes are complex chiral structures and their functionality tends to interact, therefore, differently with two enantiomers or mirror images of one molecule as already mentioned in section 2.3. Pharmaceutical intermediates often incorporate one or more stereocenters. To guarantee the right therapeutic treatment specific interactions between drug and target (*e.g.* receptor/enzyme) should take place. In general the enantiomeric selectivity is valid for many molecules that interact with different organs in our body, like those responsible for taste or odor.

Synthesis becomes more complex when more stereocenters are present in the final product. Sometimes nature provides us with enantiomerically pure starting compounds, otherwise the synthesis or the work-up should be enantioselective.[1]

One way to incorporate an enantioselective reaction is to make use of kinetic resolution, *e.g.* via biocatalysis. Alternatively and more beneficially, dynamic kinetic resolution (DKR) may offer a solution by starting with a racemic mixture and ending with an enantiomerically pure product in high yields, see Figure 3.1.
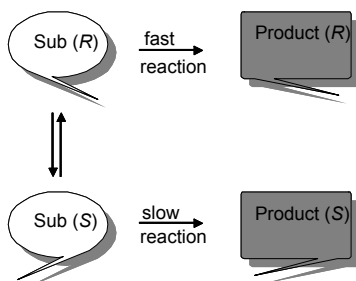


**Figure 3.1** *Overview of dynamic kinetic resolution (DKR). A combination of two processes: racemization of substrate (Sub) and kinetic resolution to product from a racemic mixture ("R" or "S").*

DKR is based on two processes: an enantioselective reaction (kinetic part) and a racemization (dynamic part) of the starting material. With DKR the racemization becomes an *in-situ* process.

The racemization of 1-phenylethanol with the aid of a ruthenium catalyst has been intensively studied by Van Buijtenen in our group; see Scheme 3.1.[2] The racemization was ultimately combined with an enzymatic kinetic resolution (with the help of Novozym 435). Additional research on the conventionally heated DKR-process has been reported in the MSc-thesis of Van Nispen.[3] A comparison with a microwave-heated experiment was also included, see Figure 3.2.
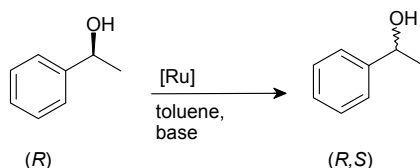
**Scheme 3.1**    *The racemization of (S)-1-phenylethanol, using a dinuclear ruthenium BINAP complex as catalyst. This catalyst needs to be activated under $O_2$-free conditions by a base at elevated temperature.*[2]
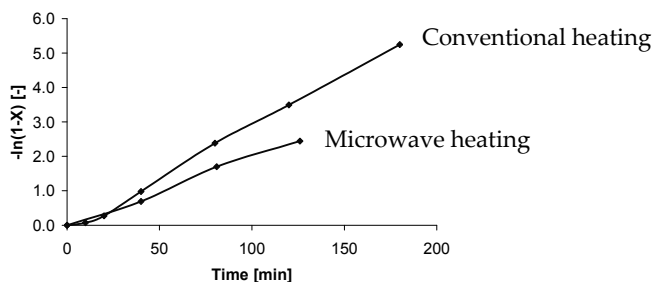


**Figure 3.2**    *Racemization of (S)-1-phenylethanol at 70 °C in the presence of 15 mol % of acetophenone performed with conventional and with microwave heating. 0.025 Mol % of catalyst was used.*[3]

Unfortunately, in the racemization of (*S*)-1-phenylethanol no rate enhancement with microwave heating was observed. Note that working under $O_2$-free conditions for microwave heating was more difficult than for conventional heating.[3]

Another option in the DKR procedure is separating the kinetic resolution step from the racemization, when these two processes impede each other (*e.g.* inhibition or deactivation). On large scale with multiple batches, implementation of the individual processes is economically feasible due to the ability of recycling waste-streams as shown in the example discussed in the next section.

## 3.2 Conventional heating

In the case of a classic resolution of *N*-acetylindoline-2-carboxylic acid, a waste stream in the industrial process contains an enriched content of the wrong enantiomer.[4,5] After a separate racemization step (Scheme 3.2 (left)), the product is reintroduced in the process, eventually leading to the pharmacologically active end product perindopril (Scheme 3.2 (right)). On the one hand a fast racemization step is preferred; on the other an easy work-up. A co-solvent or a good solvent increases

the solubility, thus improving to the rate of the racemization. However, removal of the solvent (*e.g.* through distillation) is inefficient from the time and energy perspectives. For the racemization of *N*-acetylindoline-2-carboxylic acid, *p*-xylene is selected as a solvent in view of its high boiling point, inertness and poor solubilizing power. Indirectly the high boiling point partially compensates for the poor solubility. The work-up is simplified by filtration, which is more energy effective than distillation. The actual racemization is catalyzed by acetic anhydride,[6,7] see Scheme 3.2 (left).



**Scheme 3.2**    *(left) Racemization of (R)-N-acetylindoline-2-carboxylic acid (1).*
                  *(right) Perindopril, drug for hypertension treatment.*

Acetic anhydride reacts with the acid functionality thus forming a mixed anhydride. Ring closure eliminates acetate and gives rise to an oxazolium intermediate. At this stage the chiral information is lost by keto-enol tautomerization and - due to the reversible character of this reaction - the substrate racemizes completely; see Scheme 3.3 and Figure 3.3. Other options, such as Pd-catalysis to racemize amino-acids[8-12] and racemizations in general are reviewed by Zwanenburg *et al*.[13]

In our laboratory the racemization experiments have been performed with two grades with respect to enantiomeric purity and to stereochemical identity. The initial experiments were performed using a scalemic mixture with an enantiomeric excess (ee) of 67 % (*R*). Additional experimentation was performed with the (*S*)-enantiomer (99 % ee). This study surprisingly revealed a complex process that required more detailed investigation, see Figure 3.4 for the results. On addition of the catalyst the ee initially decreases as expected, but after a certain period the ee levels off with conventional heating. The rate of racemization dependents on temperature as well as on the amount of acetic anhydride (see also section 3.3 for a mechanistic suggestion and Scheme 3.6).

**Scheme 3.3**    *Mechanism of the racemization of (R)-N-acetylindoline-2-carboxylic acid: [1] formation of mixed anhydride, [2] ring closure, [3] keto-enol tautomerization and [4] acid-base proton-shift.*
*Remark: after tautomerization the oxazolium is achiral; the reverse reaction can form either enantiomer (R or S). Only one enantiomer is depicted to make this scheme comprehensible.*



**Figure 3.3**    *Racemization of (R)-N-acetylindoline-2-carboxylic acid in p-xylene (1.35 M) with 0.1 equivalent of acetic anhydride at 130 °C with conventional heating: (left) ee vs. time for a long period and (right) ee vs. time for the initial period.*
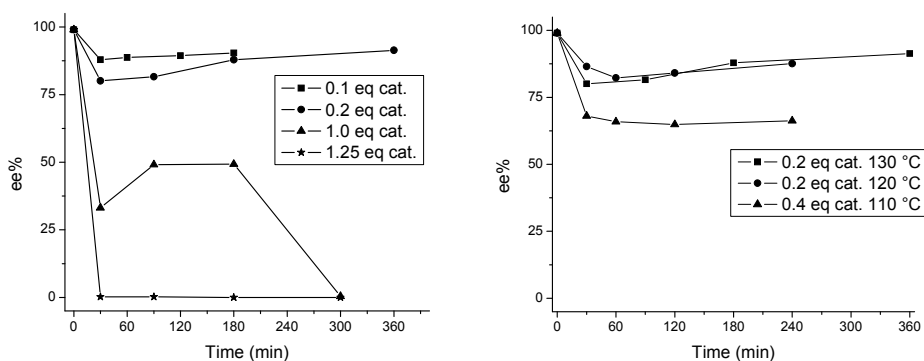
**Figure 3.4**    *Racemization of (S)-N-acetylindoline-2-carboxylic acid in p-xylene at 130 °C with conventional heating; (left) influence of the amount of acetic anhydride and (right) influence of temperature.*

Water may influence the course of the reaction due to hydrolysis of acetic anhydride. After complete hydrolysis of acetic anhydride the racemization stops. For molar ratios of water and acetic anhydride smaller than one some catalytic activity remains. However, the reaction product of hydrolysis of acetic anhydride, acetic acid, acts as a co-solvent for *N*-acetylindoline-2-carboxylic acid. Here acetic acid positively influences the rate of racemization.

If the solubility of one of the intermediates in the catalytic process is much lower than that of the actual substrate, the racemization may stop (*i.e.* deposition of an intermediate makes the racemization irreversible). Then racemization can only take place with a stoichiometric amount of acetic anhydride. The actual amount of acetic anhydride necessary for proper racemization strongly depends on the wetness of the substrate.

Since saturation is maintained during the complete racemization process and the reaction rate partly depends on the concentration of the substrate in solution, the reaction rate should increase until the enantiomeric excess has reached a value of 20 - 30 % ee representing the situation with the highest solubility (Figure 3.5).[14] For ee < 30 % the solubility seems not to be significantly dependent on ee and pseudo zero-order kinetics should be expected. The actual observations are different, because the reaction rate depends on the presence of active catalyst.
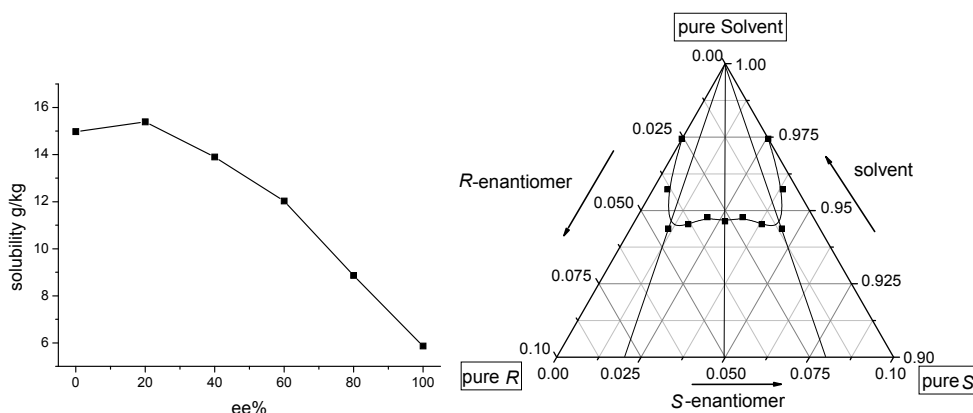
**Figure 3.5**    *(left) Solubility (g [substrate] per kg [reaction mixture]) of N-acetylindoline-2-carboxylic acid at different values of ee in p-xylene at 130 °C. (right) Ternary diagram of N-acetylindoline-2-carboxylic acid and p-xylene at 130 °C.*[14]

### Influence of the co-solvent

The racemization of *N*-acetylindoline-2-carboxylic acid using pure acetic acid as solvent has been reported.[4,5] In our case acetic acid has been applied as a co-solvent with *p*-xylene to study the role of heterogeneity. With approximately 20 wt% of acetic acid the reaction mixture becomes homogeneous. In this regime substrate concentration is at a maximum and the racemization process proceeds much faster (see Figure 3.6).
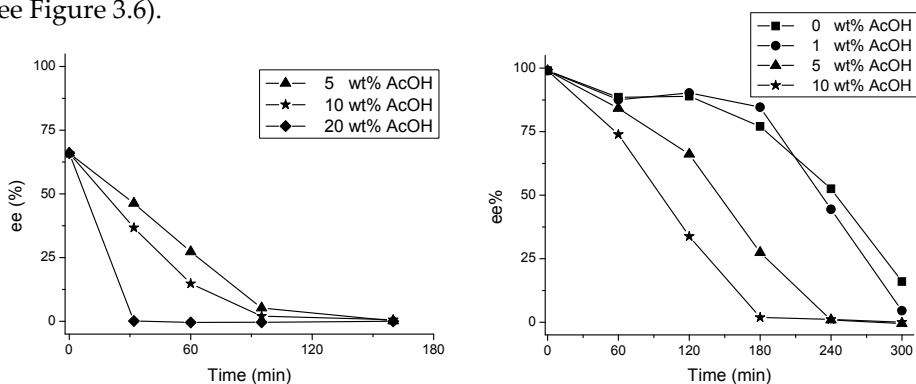


**Figure 3.6**    *(left) Racemization of (R)-N-acetylindoline-2-carboxylic acid in p-xylene at 130 °C with 0.1 molar equivalent of acetic anhydride with conventional heating; influence of the amount of co-solvent, acetic acid. (r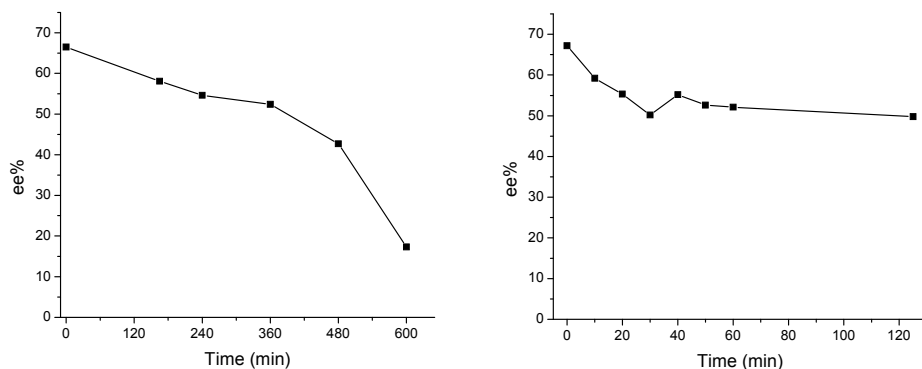ight) Racemization of (S)-N-acetylindoline-2-carboxylic acid in p-xylene at 130 °C with 0.1 molar equivalent of acetic anhydride with conventional heating; influence of the amount of co-solvent, acetic acid.*

**Influence of the temperature**

To study the influence of temperature on the racemization, the reaction was also performed at temperatures below 130 °C. This resulted in incomplete racemizations which were already depicted in Figure 3.4 (right). As mentioned before, acetic anhydride is consumed in an intermediate which seems to be irreversibly formed (*e.g.* by precipitation) at lower temperatures in the apolar solvent *p*-xylene. Increasing the bulk temperature or improving solubility in general enables the possibility to complete the racemization.

In addition, the effect of the temperature on the racemization of *N*-acetyl-phenylalanine, which is analogous to *N*-acetylindoline-2-carboxylic acid, is also illustrated in the next section. This reaction appears to have a broader temperature range in which racemization occurs. Nevertheless, here also inhibition is observed in the case of temperatures below 70 °C.

**Influence of the substrates**

To understand the peculiar mechanistic phenomena observed in the racemization of *N*-acetylindoline-2-carboxylic acid and to gain more insight into the related microwave effect (see section 3.3), other chiral *N*-acetyl amino acids were synthesized to investigate their racemization behavior. Two substrates in which formally the CH2-Ph and NH-Ph bands were cleaved have been selected, *i.e. N*-acetylphenylalanine (**2**) and *N*-acetyl-*N*-phenyl-alanine (**3**), see Scheme 3.4.
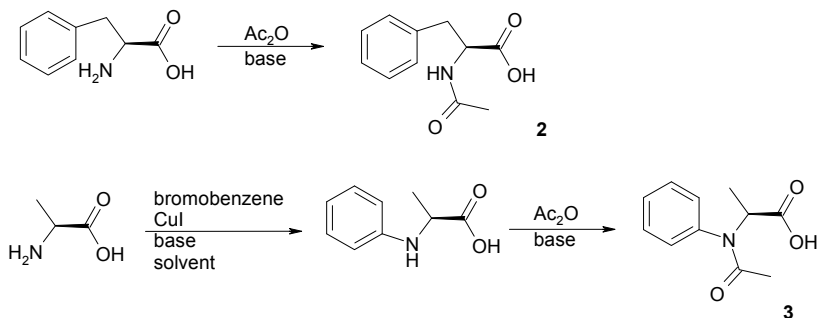


**Scheme 3.4**    *Proposed synthesis of N-acetylphenylalanine (2) and N-acetyl-N-phenyl-alanine (3) as two analogues of (S)-N-acetylindoline-2-carboxylic acid; based on (S)-phenylalanine (top) and (S)-alanine (bottom).*

*N*-Acetylphenylalanine and *N*-acetyl-*N*-phenyl-alanine could in principle be synthesized from optically pure natural amino acids as starting materials. Acetylation of (*S*)-phenylalanine is a straightforward procedure to obtain the first

substrate **2**. Unfortunately, it was not possible to isolate (*S*)-*N*-acetyl-*N*-phenyl alanine (**3**) in sufficient amounts by an Ullmann type of coupling.

Under benchmark conditions (*i.e.* 130 °C) the racemization of (*S*)-*N*-acetyl-phenylalanine (**2**) was complete within 5 minutes. For practical reasons the temperature was lowered to a value of 85 °C (Figure 3.7).

The heat of solution ($\Delta_{soln}H°$) of *N*-acetylphenylalanine for the racemic mixture and for the enantiomerically pure compound were both calculated (see equation 3.1, *Sol* stands for solubility; [mol.L$^{-1}$]) as approximately 85 kJ/mol for both cases in *p*-xylene.[15] The large value of $\Delta_{soln}H°$ indicates that the influence of temperature on the rate of racemization is considerably governed by the solubility of *N*-acetylphenylalanine.[16] In comparison, the heat of dissolution ($\Delta_{soln}H°$) for *N*-acetylindoline-2-carboxylic acid was calculated to be 75 kJ/mol in *p*-xylene representing also a high value.[15]

$$\ln Sol = constant \; -\frac{\Delta_{soln}H°}{RT} \tag{3.1}$$

Racemization appears to be fast and hence measurements in the liquid phase show only the presence of a racemic mixture for the two substrates.
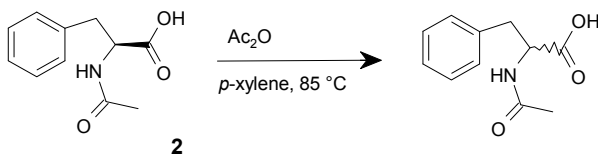


**Scheme 3.5**   *Racemization of (S)-N-acetylphenylalanine (2) with the aid of 0.1 molar equivalent of acetic anhydride.*
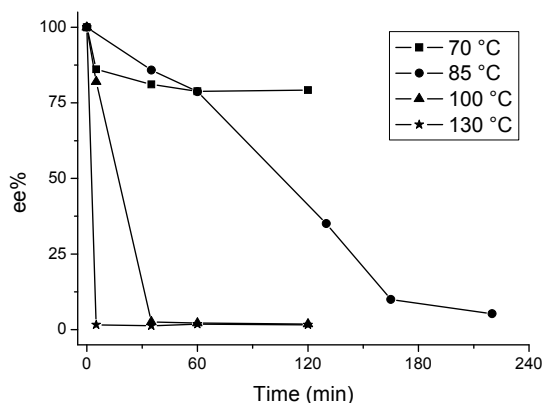


**Figure 3.7**   *Racemization of (S)-N-acetylphenylalanine (2) in p-xylene at various temperatures with conventional heating.*

## 3.3 Microwave heating

As described in chapter 2, a direct comparison between conventional and microwave heating is only possible when identical reaction conditions except the method of heating are selected. In the present work the microwave effect ($f_{MW}$) has been defined as the ratio of the initial reaction rate[‡] with microwave heating ($r_{MW}$)$_{t=0}$ and the initial rate[‡] with conventional heating ($r_{CH}$)$_{t=0}$, see equation 3.2. Three reaction parameters (*i.e.* temperature, amount of co-solvent and substrate) have been varied as described in section 3.2. Each figure in this section shows time-conversion histories under conventional and microwave heating conditions.

$$f_{MW} = \left( \frac{r_{MW}}{r_{CH}} \right)_{t=0} \tag{3.2}$$

The results in Figure 3.4 (left) demonstrate that the racemization seems to stop when using smaller amounts of acetic anhydride. Duplicates illustrate the same behavior. However - to our surprise - when the same reaction mixture was transferred from an oil bath to the microwave oven racemization starts up again (Figure 3.8).
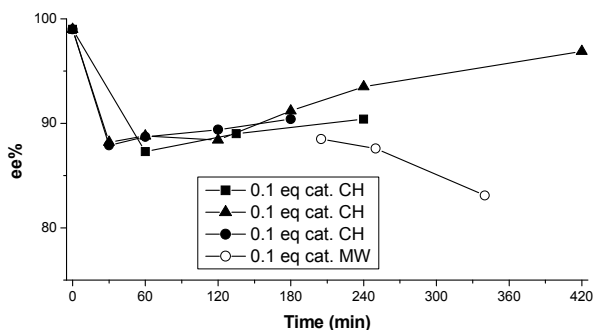


**Figure 3.8**    *Racemization of (S)-N-acetylindoline-2-carboxylic acid with 0.1 molar equivalent of acetic anhydride at 130 °C with conventional heating; duplicate (—▲—) and an extra-dried batch (—■—). After three hours the reaction vessel was transferred to continue the reaction in the microwave oven (—○—).*

---

[‡] *Initial period is after a possible induction period and is measured over at least a conversion difference of 10 %.*

This observation suggests that the molecular species that stops the racemization under conventional heating is actually an intermediate in the process. The previously mentioned intermediate in section 3.2, which has temporarily consumed all of the acetic anhydride, is (partly) dissolved or reactivated by microwave heating. Given the relationship between enantiomeric excess at the plateau and the amount of acetic anhydride (Figure 3.4 (left)) the intermediate presumably originates from a (potentially racemized) substrate and two acetic anhydrides. One anhydride is used to form the oxazolium intermediate in the first part and another anhydride is used to form an eventually insoluble or inactive structure which inhibits the overall process of racemization (Scheme 3.6). Only an increase in temperature or a larger amount of co-solvent can shift the equilibrium back to complete the racemization. The solubility does not play a role at lower % ee due to a higher solubility of the racemate (see Figure 3.5).
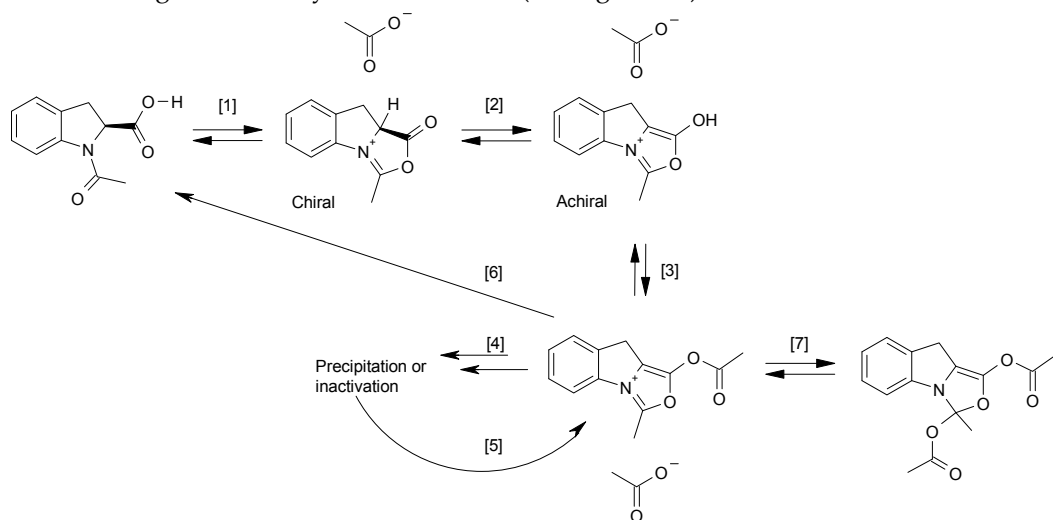


**Scheme 3.6**  *Inhibition of racemization: [1] formation of oxazolium intermediate with acetic anhydride, [2] keto-enol tautomerization, [3] formation of oxazolium-acetate with acetic anhydride, [4] precipitation or inactivation of intermediate, [5] dissolution of intermediate by e.g. microwave heating and [6] addition of water leading to regeneration of the substrate, [7] acetate bonded to intermediate (covalent or ionic).*
*Remark: after tautomerization the oxazolium is achiral; the reverse reaction can give either enantiomer (R or S). Only one enantiomer is depicted to make this scheme comprehensible.*

Shortly after addition of acetic anhydride the solubility of *N*-acetylindoline-2-carboxylic acid temporarily increases. Thereafter, two processes of precipitation and simultaneous racemization allow the % ee to slightly increase with respect to the plateau level. The (*S*)-enantiomer selectively precipitates in favor of the (*R*)-enantiomer, due to the presence of a majority of (*S*)-enantiomer crystals. After work-up with water the insoluble structure is dissociated into (*R*) or (*S*)-*N*-acetylindoline-2-carboxylic acid. By applying solid-state NMR the intermediate has been compared with the enantiomerically pure substrate and the racemic product. The spectrum shows another set of peaks, but no conclusive evidence can be produced from this analysis.

The increase of % ee in time could, however, not be explained by the method of sampling, which was checked by comparing representative samples with the direct work-up of a whole batch. An increase of % ee in a dynamic system during a longer period of days has also been demonstrated by Blackmond *et al*.[17] The increase in ee is explained by a slight enantioimbalance which directs the trend to a single chiral solid state.

**Influence of a co-solvent**

The addition of acetic acid as a co-solvent diminishes the heterogeneity of the reaction mixture. During conventional heating this induced a drastic increase of the reaction rate (see Figure 3.6). With microwave heating reaction rates were not significantly different for all solvent compositions, see Figure 3.9.
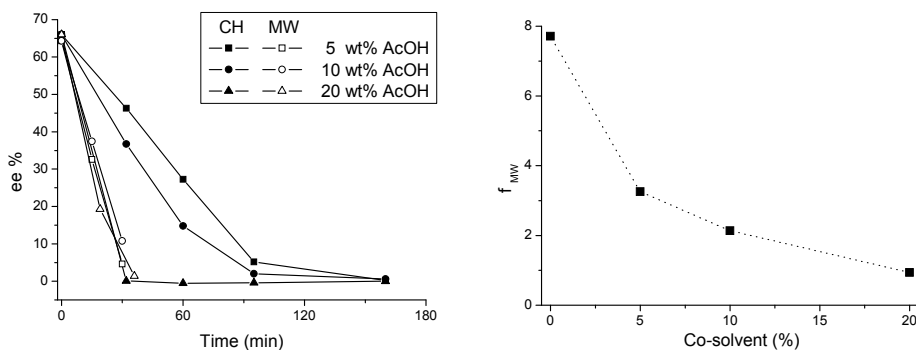


**Figure 3.9**       *Racemization of (R)-N-acetylindoline-2-carboxylic acid with 0.1 molar equivalent of acetic anhydride in various p-xylene/acetic acid mixtures at 130 °C for (left) conventional (CH) and microwave heating (MW) conditions and (right) influence of solvent composition on the microwave effect ($f_{MW}$).*

As soon as the reaction mixture becomes homogeneous (20 wt% co-solvent) no differences were observed between conventional and microwave heating. The microwave effect is strong in the absence of acetic acid as co-solvent ($f_{MW}$ = 8), while it strongly reduces upon addition of acetic acid. Hence the effect vanishes when homogeneity is reached ($f_{MW}$ = 1), see Figure 3.9 (right).

**Influence of the substrates**
(*S*)-*N*-acetylphenylalanine (Scheme 3.5) also showed an enhancement of the reaction rate at 70 and 85 °C with microwave heating, see Figure 3.10 (left). The appearance of a microwave effect in the racemization of *N*-acetyl amino acids appears not to be a "one-case-show". At 85 °C in pure *p*-xylene racemization is observed for both heating techniques while observing a strong microwave effect ($f_{MW}$ = 5.8). However, at 70 °C the racemization only continues for microwave heating. At this temperature (70 °C) the microwave effect is theoretically very high, see Figure 3.10 (right).
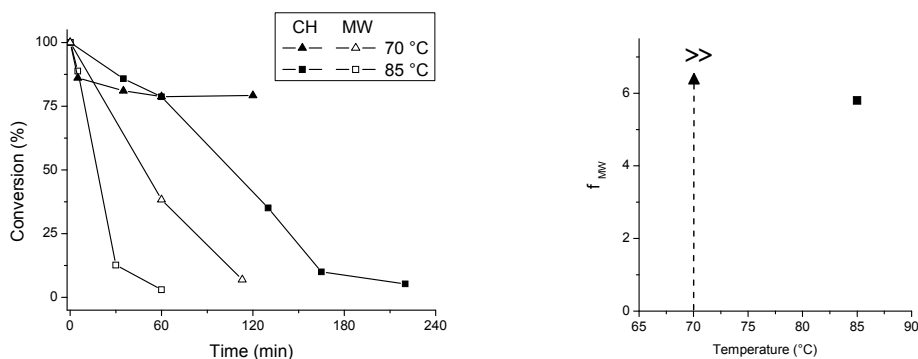


**Figure 3.10**    *Racemization of (S)-N-acetylphenylalanine at 70 °C and 85 °C for (left) conventional (CH) and microwave heating (MW) and (right) influence of temperature on microwave effect (f$_{MW}$).*

## 3.4 Discussion & Conclusion

From chapter 2 it may appear unlikely that a microwave effect really exists. Careful comparison of the reaction conditions in the cases described in chapter 2 demonstrated that no differences in reaction rates could be observed. Under identical conditions reaction rate enhancements could not be detected with homogeneous mixtures by switching from conventional heating to microwave

irradiation. However, for heterogeneous reactions differences were observed between both heating techniques. During the racemization of *N*-acetylindoline-2-carboxylic acid and *N*-acetylphenylalanine real microwave effects have indeed been observed under various conditions. Changing the reaction conditions (*e.g.* temperature or amount of co-solvent) had, however, a direct influence on the magnitude of the microwave effects. It seems that there is a correlation between the heterogeneity of the system and the observed microwave effects. The racemization of *N*-acetyl amino acids in *p*-xylene occurs at or near the surface of the solid particles. In solution only a racemic mixture could be measured throughout the racemization.

Neither the (pure) solvent (*p*-xylene; loss tangent ≈ 0.0011)[18] nor the solid (*N*-acetyl amino acid) absorb the microwaves efficiently.[18] Although the existence of hot-spots is unlikely to occur in this situation, selective heating at the interface between solid and liquid would be more plausible (see also chapter 4). Mechanistically nothing changes. However, solubilities may increase as a result of selective heating. Small changes in temperature also have a large influence on the solubility of the *N*-acetyl amino acid, according to a high heat of solution ($\Delta_{soln}H° = 75\text{-}85$ kJ/mol). For example, an increase of 2 °C enhances the solubility with 15 % and an increase of 10 °C doubles the solubility of *N*-acetylphenylalanine in *p*-xylene.

## 3.5 Experimental section

*All microwave-heated experiments were performed in a MicroSynth of Milestone srl., Italy with internal fiber-optic temperature measurement. For other details, see experimental section in chapter 2. For these reactions strong magnetic stirring has proven to be sufficient compared to overhead stirring.*

***Racemization of wet (R)-N-acetylindoline-2-carboxylic acid (1) of 66 %ee:*** *A round-bottomed flask was charged with wet (~5 wt% $H_2O$) (R)-N-acetylindoline-2-carboxylic acid (1.78 g, 8.7 mmol, 66 %ee R) and p-xylene (5.5 g). This heterogeneous mixture was heated in a Dean–Stark distillation setup to azeotropically remove water (~1.5 mL distillate). The total mass of the reaction mixture was adjusted at 7.0 g with solvent, and the mixture was heated to 130 °C in the Milestone microwave oven (average power: 82 W / max: 300 W). (A Weflon bar was added during microwave heating at 0 wt% co-solvent). Then acetic anhydride (100 µL, 1.1 mmol) was added. After 2 h water (100 µL) was added, and via a Dean–Stark distillation setup p-xylene/water/acetic acid was distilled from the reaction mixture (~2.5 mL distillate). After cooling the solid was filtered and washed twice with p-xylene (2 mL) and dried under reduced pressure at 50 °C. The reaction was monitored by quenching a sample (~50 mg) with water (25 µL) to neutralize*

*the anhydride. The samples were dissolved in a mixture of formic acid (3 mL), isopropanol (25 mL) and n-hexane (72 mL) and analyzed by HPLC, chiral column (Daicel, Chiracel OD) with an eluent composed of formic acid (1 v%), isopropanol (10 v%) and n-hexane (89 v%). The yield after work-up was 1.35 g (76 %). The same procedure was followed for the conventionally heated experiment by substituting microwave irradiation by oil bath heating. Yield after work-up: 1.62 g (91 %).*

***Racemization of (S)-N-acetylindoline-2-carboxylic acid (MW) of 99 %ee.*** *A round-bottomed flask was charged with dry (S)-N-acetylindoline-2-carboxylic acid (1.78 g, 8.7 mmol, 99 %ee S) and p-xylene (5.5 g). The mixture was heated to 130 °C in the Milestone microwave oven. (A Weflon bar was added during microwave heating at 0 wt% co-solvent). Then acetic anhydride (100 µL, 1.1 mmol) was added. After 2 h water (100 µL) was added, and p-xylene/water/acetic acid was distilled from the reaction mixture. After cooling the solid was filtered and washed twice with p-xylene (2 mL) and dried under reduced pressure at 50 °C. The reaction was monitored by quenching a sample (~50 mg) with water (25 µL) to neutralize the anhydride. The samples were dissolved in a mixture of formic acid (3 mL), isopropanol (25 mL) and n-hexane (72 mL) and analyzed by HPLC, chiral column (Daicel, Chiracel OD) with an eluent composed of formic acid (1 v%), isopropanol (10 v%) and n-hexane (89 v%). The yield after work-up was 1.35 g (76 %). The same procedure was followed for the conventionally heated experiment substituting microwave irradiation with oil-bath heating.*

***N-Acetyl-(S)-phenylalanine (2):***[10] *A round-bottomed flask was charged with (S)-phenylalanine (19.8 g, 0.12 mol) and an aqueous solution (30 mL) of NaOH (4,8 g, 0.12 mol). To this mixture acetic anhydride (12.24 g, 0.12 mol) was added drop-wise with the simultaneous addition of an aqueous solution (15 mL) of NaOH (4,8 g, 0.12 mol) under vigorous stirring and at room temperature. The temperature was kept below 30 °C and pH was maintained around 10. After 30 min. another amount of acetic anhydride (12.24 g, 0.12 mol) was added dropwise with simultaneous addition of an aqueous solution (15 mL) of NaOH (4,8 g, 0.12 mol) under vigorous stirring and at room temperature. This mixture was extracted with ethyl acetate (100 mL), pH was set at 6 with 6 M HCl under vigorous stirring with cooling in an ice-bath. The extraction procedure was repeated for pH values set at 5, 4 and 3. The organic layers were combined and subsequently washed with brine (100 mL) and demi-water (50 mL). Organic solvent was removed under reduced pressure. The yield after work-up was 21.0 g (84 %). $^1$H-NMR (CD$_3$OD, 400 MHz) typical signals δ (ppm) 7.51 (m, 5H, Ar-H), 4.92 (m, 1H, CH-CH$_2$), 3.45 (dd, 1H, CH-CH$_2$), 3.20 (dd, 1H, CH-CH$_2$), 2.15 (s, 3H, CO-CH$_3$); [α]$^{23}_D$ +29.7° (c = 10, MeOH), literature[19] [α]$^{23}_D$ +33° (c = 10, MeOH).*

***N-Phenyl-(S)-alanine:***[20] *A round-bottomed flask was charged with (S)-alanine (28.51 g, 0.32 mol), CuI (6.09 g, 32 mmol), $K_3PO_4$ (135.6 g, 0.64 mol), bromobenzene (39.25 g, 0.25 mol), diethanolamine (60 mL) and water (200 mL). The reaction mixture was heated at 90°C for 40 h under nitrogen atmosphere. Thereafter, the mixture was quenched on 1 kg ice and was extracted with ethyl acetate (500 mL), pH was set at 6 with 6 M HCl under vigorous stirring with cooling in an ice-bath. The extraction procedure was repeated for pH values set at 5, 4 and 3. The organic layers were combined and subsequently washed with brine (500 mL) and demi-water (500 mL). The organic solvent was removed under reduced pressure. The yield after work-up was 26.2 g (63 %). *$^1$H-NMR (CD$_3$OD, 400 MHz) typical signals δ (ppm) 7.37 + 6.90 (m, 5H, Ar-*H*), 4.30 (q, 1H, C*H*-CH$_3$), 1.73 (d, 3H, CH-C*H$_3$*). HPLC-Chiracel OD (for conditions see first procedure); 50 % ee.*

***N-Acetyl-N-phenyl-alanine (3):***[10,21] *A round-bottomed flask was charged with N-phenyl-alanine (23.28 g, 0.14 mol) and triethylamine (85.0 g, 0.84 mol). At room temperature acetic anhydride (14.3 g, 0.14 mol) was added dropwise. The reaction mixture was kept at room temperature for 3 h. Thereafter, the mixture was quenched with water (10 g) and extracted with ethyl acetate (250 mL), pH was set at 5 with 6 M HCl under vigorous stirring with cooling in an ice-bath. The extraction procedure was repeated for pH values set at 4 and 3. The organic layers were combined and subsequently washed with brine (100 mL) and demi-water (100 mL). Yield: 5.7 g (20%). *$^1$H-NMR (CD$_3$OD, 400 MHz) typical signals δ (ppm) 7.38 (m, 5H, Ar-*H*), 4.93 (q, 1H, C*H*-CH$_3$), 1.86 (s, 3H, CO-C*H$_3$*), 1.28 (d, 3H, CH-C*H$_3$*). HPLC-Chiracel OD (for conditions see first procedure); 12 % ee.*

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14   Solubility is determined by weight difference (before and after drying) of supernatant of *N*-acetyl amino acid in *p*-xylene (at 130 °C) after vigorous mixing of a saturated solution during 5 min and 16 h.

15   Solubility in *p*-xylene of (*S*)-*N*-acetylphenylalanine is 3.2, 4.1 and 27 mmol/l at 85, 100 and 115 °C; of (*R,S*)-*N*-acetylphenylalanine is 2.3, 5.4 and 21 mmol/l at 85, 100 and 115 °C and of (*R,S*)-*N*-acetylindoline-2-carboxylic acid is 4.1, 8.9 and 24.4 mmol/l at 102, 116 and 132 °C, respectively.

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# Chapter 4

# 4

# Nucleophilic addition of isocytosines to isocyanates

# Abstract

The combination of isocytosines and isocyanates leads to building blocks for supramolecular polymers.

Nucleophilic additions of various C6-substituted isocytosines (methyl, ethyl, isopropyl and phenyl) to (di)isocyanates have been investigated. The heterogeneous reaction mixtures again showed reaction rate enhancements with microwave heating, comparable to the examples described in chapter 3. Variation of substituents, temperature and amount of a co-solvent essentially influenced the magnitude of the microwave effects. Based on the solubility and reactivity of various C6-substituted homologues of isocytosine the magnitude of the microwave effect could be predicted.

The diffusion layer near the solid surface is the area where selective heating by microwaves is believed to occur. As a result locally higher temperatures increase solubility and reaction rates while, in contrast, a relatively lower bulk temperature is measured.

In brief, the observed microwave effects have a thermal rationale based on direct, fast and selective heating. This effect is not reproducible by conventional heating.

4

## 4.1 Introduction

In the previous chapter the racemization of *N*-acetyl amino acids revealed the importance of a heterogeneous character to observe a microwave effect. Given the heterogeneity of the nucleophilic addition of isocytosines to isocyanates (Scheme 4.1) – starting material isocytosine and end product are practically insoluble – this process seemed to be a valuable candidate for a successive study.
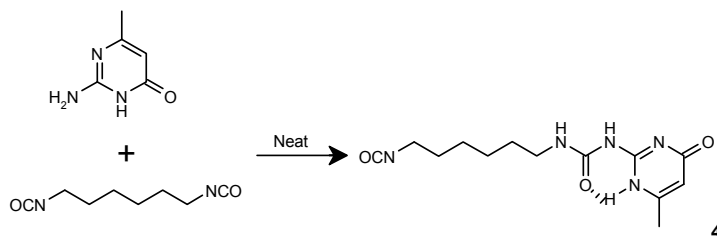


**Scheme 4.1**    *Reaction of 6-methylisocytosine with hexamethylenediisocyanate to synthesize a self-complementary UPy moiety.*

The addition of an amine to an isocyanate leads to a urea functionality, which is capable of undergoing intermolecular hydrogen bonding. In case of isocytosine this leads to a self-complementary ureidopyrimidinone (UPy) moiety that is characterized by quadruple hydrogen bonding. A monofunctional UPy dimerizes and a bifunctional UPy leads to a supramolecular polymer. The monofunctional Upy - with a reactive terminal isocyanate – can be used for post-polymerizations (*e.g.* polymeric alcohols). The introduction of two ureidopyrimidinone moieties in one molecule makes the latter suitable to act as a monomer for supramolecular polymerization (Figure 4.1).
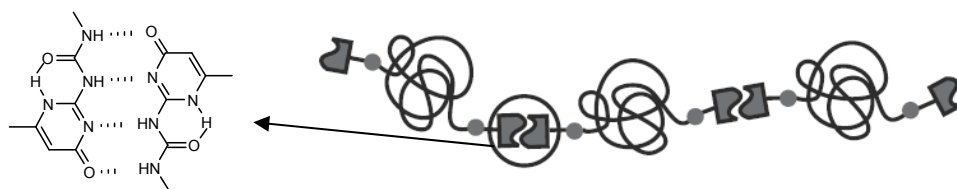


**Figure 4.1**    *Incorporation of two ureidopyrimidinone (UPy) moieties in a block co-polymer leads to a macromonomer for supramolecular polymerization (right part of Figure from reference 1).*

This work has been initiated and studied in detail by the groups of Meijer and Sijbesma, culminating in a commercial product line supplied by SupraPolix B.V.[2,3,‡]

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‡ SupraPolix B.V., Eindhoven, The Netherlands.

Potential applications are in the field of adhesives[4], printing[5], cosmetics[6], personal care[7] and coatings[8].

With the knowledge gained in our group (Applied Organic Chemistry) from a previous study,[9] it would be of interest to investigate the synthesis of the ureidopyrimidinone moiety, in terms of rate and mono-selectivity with microwave heating in comparison with conventional heating. Most importantly, variations in the reaction parameters may enable to find a rationale for potential differences between both heating methods.

## 4.2 Conventional heating

Although all chemical reactions were performed with conventional as well as with microwave heating, first the conventional approach by oil-bath heating is reported in this section. The actual careful comparison between conventional heating and microwave heating is made in section 4.3.

The reaction parameters (*e.g.* temperature or co-solvent) of the addition of 6-methylisocytosine to hexamethylene diisocyanate (HDI), acting in the same time as solvent, have been thoroughly investigated in our group. The optimal reaction conditions of a process scale-up study were applied in a 10 L multipurpose semi-batchwise operated stirred-tank reactor.[9,‡] The results of the scale-up study[9] have demonstrated the occurrence of mass transfer limitations at temperatures exceeding 100 °C (see Figure 4.2).
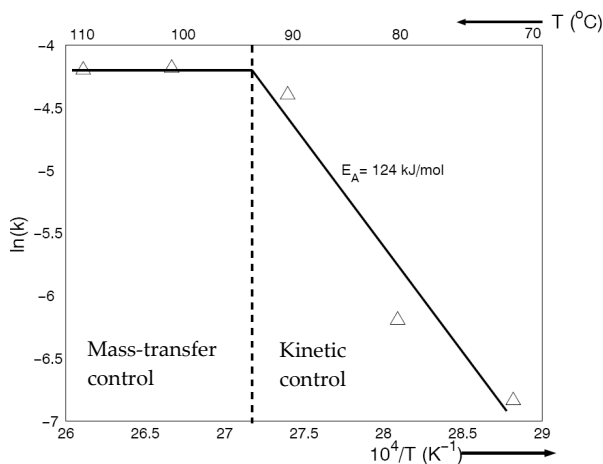


**Figure 4.2**    *Temperature effect on the overall rate coefficient adopting pseudo first-order kinetics [reference 9]*

‡ Equipment from Belatec AG, Wintersingen, Switzerland.

Below 100 °C mono-adduct is selectively formed. Mono-addition, essential for further down-stream chemistry, is rationalized by the limited solubility of 6-methylisocytosine in HDI and by the presence of an excess of HDI. After mono-addition the product has an even lower solubility preventing twofold addition.

**Influence of temperature**

Time-conversion experiments were performed at three temperatures to find ideal conditions for reaching completion within a time span of one to three hours, see Figure 4.3. This duration was selected from the prospect of further process scaling-up.
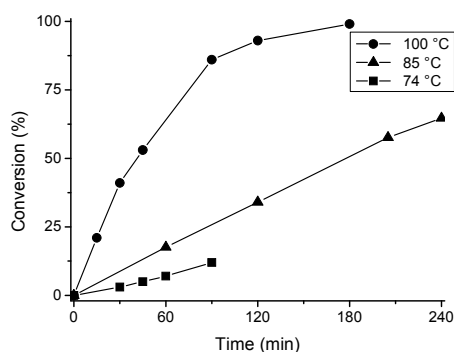


**Figure 4.3**    *Nucleophilic addition of 6-methylisocytosine to hexamethylene diisocyanate (7.5 eq.) at 74 °C, 85 °C and 100 °C under neat conditions.*

In the first period after the start of the reaction, up to conversions of approximately 75 %, the reaction nearly obeys (pseudo) zero-order kinetics, see Figure 4.3. The substrate is sparingly soluble and hence is present in solution at a constant, very low concentration. HDI, on the contrary, is as solvent and reactant initially present in 7.5 molar excess and is, therefore, also constant throughout the reaction.

An accurate value of the solubility of 6-methylisocytosine in the reaction mixture could not be determined and therefore absolute values for the rate coefficient could not be produced from the Arrhenius equation (see Equation 4.1-a).[‡]

$$k = A \cdot e^{\frac{-E_a}{RT}}$$  **(4.1-a)**

$$r = C_0 \cdot \frac{dx}{dt} = A' \cdot e^{\frac{-E_a}{RT}}$$

$$\ln\left(\frac{dx}{dt}\bigg|_{t=0}\right) = \ln\left(\frac{A'}{C_0}\right) - \frac{E_{a,apparent}}{RT}$$  **(4.1-b)**

---

[‡] $E_{a, apparent}$ = apparent activation energy.

Instead of introducing the k-value as the rate constant in Equation 4.1-a, $(r_{CH})_{t=0}$ an initial reaction rate was applied to estimate the apparent activation energy,[10] see Equation 4.1-b. The initial conversion rate $[d(x)/d(t)]_{t=0}$ is expressed in $[min^{-1}]$. An overview of the initial conversion rates is given in Table 4.1 depending on three temperatures and some weight fractions of co-solvent NMP.

**Table 4.1** *Overview of initial conversion rates ($r_{CH}$) of nucleophilic addition of 6-methylisocytosine to hexamethylene diisocyanate at different temperatures and some weight fractions of co-solvent (NMP) under conventional heating conditions.*

| entry | | conversion rate | | |
|---|---|---|---|---|
| | *temperature* | without co-solvent* | 1 wt% NMP* | 5 wt% NMP* |
| 1 | 74 °C | **1.2** | **3.3** | **9.5** |
| 2 | 85 °C | **2.8** | **4.8** | **14.9** |
| 3 | 100 °C | **12.5** | **13.7** | **29.1** |

* $[10^{-3}.min^{-1}]$

**Influence of a co-solvent**

In an additional series of experiments it was found that the heterogeneity could be influenced by addition of a co-solvent (see Table 4.1 and Figure 4.4). Reducing the heterogeneity increased the reaction rate as expected. *N*-Methyl-pyrrolidinone (NMP) was selected as a co-solvent based on earlier work.[9]
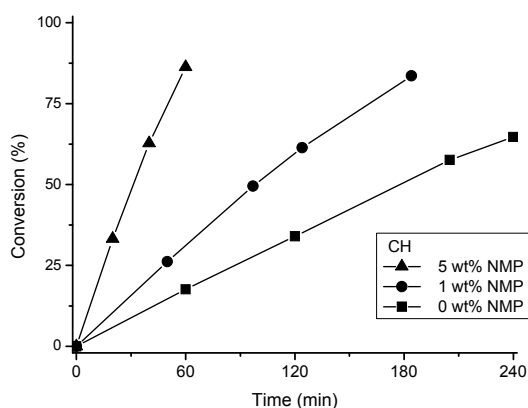


**Figure 4.4** *Nucleophilic addition of 6-methylisocytosine to hexamethylene-diisocyanate in the presence of co-solvent (NMP) at 85 °C with conventional heating (CH).*

**Scope with various substrates and reagents**

To broaden the scope of the addition of 6-methylisocytosine to hexamethylene-diisocyanate, other substrates and isocyanates were selected. Various C6-substituted isocytosines were synthesized (Scheme 4.2).[11] Additionally, HDI was replaced in the reaction with 6-methylisocytosine by *n*-hexylisocyanate (HI, Scheme 4.3).
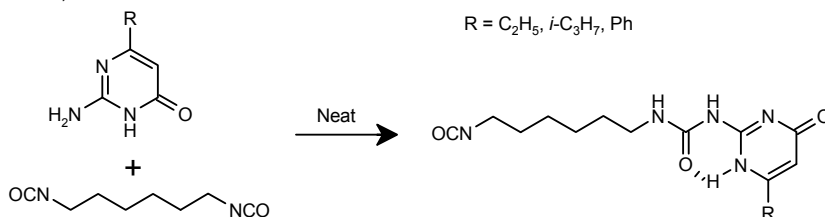


**Scheme 4.2**    *Nucleophilic addition of C6-substituted isocytosines to hexamethylene-diisocyanate.*
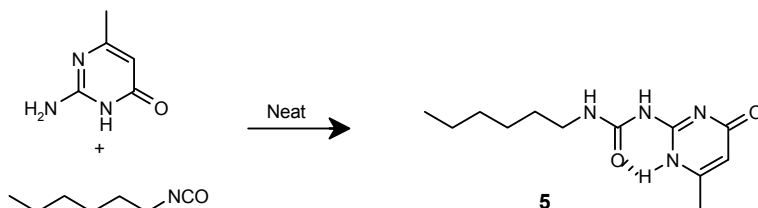


**Scheme 4.3**    *Nucleophilic addition of 6-methylisocytosine to n-hexylisocyanate.*

The use of mono-functionalized isocyanates (Scheme 4.3) automatically overcomes the possibility of twofold addition. With respect to the reaction with the diisocyanate, only a small change in solubility of isocytosine and, therefore, in conversion rate can be expected. During preliminary experimentation the addition of 6-methylisocytosine to HI revealed the significant influence of an impurity, leading to irreproducible time-conversion histories. A striking difference in reaction rate was observed between an aged, open bottle of HI and an unopened one.
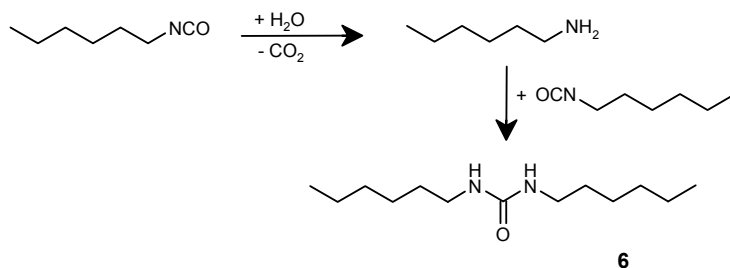


**Scheme 4.4**    *Reaction of n-hexylisocyanate (HI) with water (< 1 eq.).*

When HI from a new bottle was taken, the reaction needed more time for completion than in the case of the opened bottle. A solid precipitate in the aged bottle was identified as *N,N*-dihexylurea. This compound results from a reaction of hexylisocyanate with water, see Scheme 4.4. The influence of water on the reaction as depicted in Scheme 4.4 was not detectable nor was the occurrence of an analogous impurity in HDI.

At room temperature *N,N*-dihexylurea is a solid, but at the reactor temperatures used, it has melted and this liquid phase acted as a co-solvent. When *N,N*-dihexylurea was subsequently deliberately added to the reaction of 6-methylisocytosine with HI, reaction rates significantly enhanced, see Figure 4.5. Similar rate enhancements were observed with the addition of *N*-methylpyrrolidinone as a co-solvent.
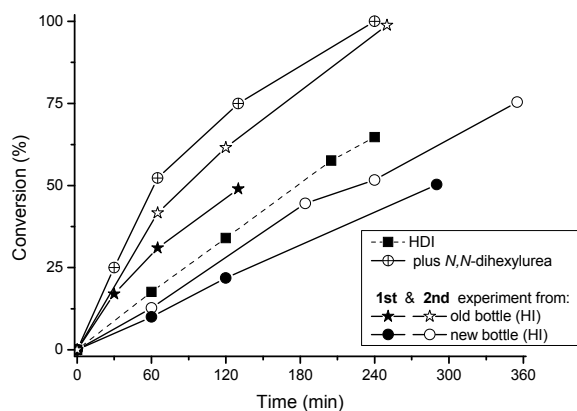


**Figure 4.5**    *Nucleophilic addition of 6-methylisocytosine to n-hexylisocyanate (HI) of different grades at 85 °C compared to the addition of 6-methyl-isocytosine to hexamethylenediisocyanate (HDI). (N,N-dihexylurea was added to fresh HI).*

Variation of the substituent at the 6-position of isocytosine was expected to largely influence its solubility[12] and as a consequence the overall reaction rate as explained earlier (*Influence of a co-solvent*). The results of the relationship between various substituents at the 6-position and the solubility or overall reaction rate are listed in Table 4.2.

Although the solubility could not be measured directly in HDI, the solubility was visually categorized and measured in two other solvents, *N,N*-dimethylacetamide (DMA) and 1,4-dioxane.

**Table 4.2**    *Outcome of varying substitutions at the C6-position of isocytosine with respect to solubility and overall reaction rate with the addition to HDI.*

| entry | substituent | sol. in DMA [μmol/l]* | sol. in 1,4-dioxane [μmol/l]* | overall reaction rate |
|---|---|---|---|---|
| 1 | methyl | 168 | < 0.1 | low |
| 2 | ethyl | 555 | 10.1 | medium |
| 3 | isopropyl | 1232 | 27.9 | medium |
| 4 | phenyl | 1079 | 40.5 | higher |

* *Solubility at 85 °C*

The polarity of these solvents was chosen above (DMA) and below (1,4-dioxane) that of HDI. Ranking the various alkylated isocytosines with respect to solubility explains an increase in reaction rate. However, the selectivity and reactivity of 6-phenylisocytosine differ significantly from those of 6-isopropylisocytosine with a comparable solubility. A plausible rationale for this behavior may relate either to the product solubility, or to the keto-enol tautomerization of the isocytosines (see Scheme 4.6) that may influence the intrinsic reaction rate of the amine functionality, respectively.

The solubilities of the methyl, ethyl, isopropyl and phenyl single addition products in 1,4-dioxane are < 0.10; < 0.10; 67.2 and 31.5 μmol/l at 85 °C, respectively. The higher the solubility of the single addition product the lower the selectivity, due to potentially twofold addition (Scheme 4.5).
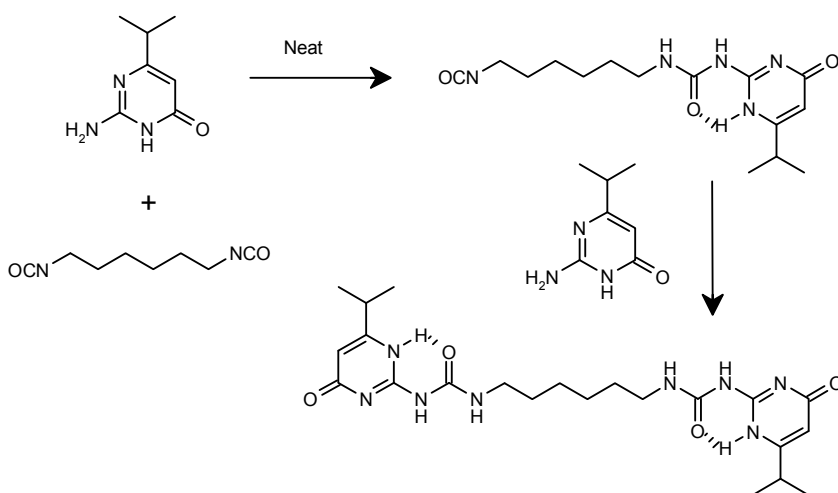


**Scheme 4.5**    *Single and twofold addition of 6-isopropylisocytosine to hexamethylene-diisocyanate.*

So in the aliphatic series, the reaction rate reflects the solubility of the isocytosines and the selectivity decreases from methyl, ethyl to isopropyl. 6-Phenylisocytosine is, however, exceptional since the solubility of the starting material is relatively high, while the mono-adduct is less soluble than the starting material.

In general, isocytosines may be represented by three interconverting tautomers (Scheme 4.6). Calculations on the charge separation for each tautomer might explain the higher reaction rate of the 6-phenylisocytosine.
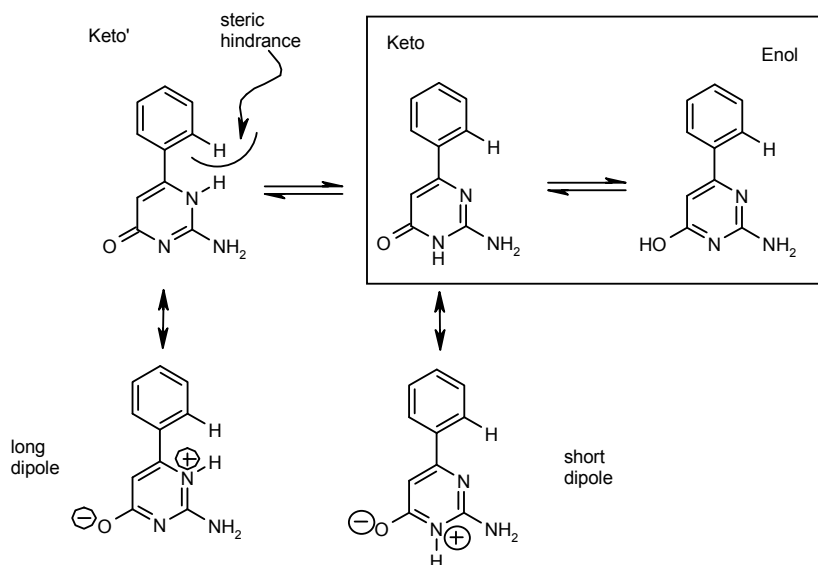


**Scheme 4.6**    *Keto-enol tautomerization of 6-phenylisocytosine.*

The aberrant profile of 6-phenylisocytosine may relate to its preference for the enol form and the concomitant enhanced nucleophilicity of the amine function.

However, extended Hückel calculations with the MM2[14] and MMFF94[14] models did not unequivocally rationalize the difference in reactivity between 6-phenylisocytiosine and 6-isopropylisocytosine.

An extended (IR-)study on the keto-enol tautomerization for ureidopyrimidinones demonstrated a favor towards the enol tautomer with electronegative substituents on the C6-position.[13]

Fortunately, IR-measurements showed indeed a higher absorption wavenumber for the $NH_2$ band (blue-shift / more nucleophilic) when 6-phenylisocytosine was

compared with 6-isopropylisocytosine (Table 4.3). This difference in the location of the NH$_2$ band was not observed among the three alkyl analogues.

**Table 4.3** *Some typical values of absorption bands in the IR-spectra of 6-isopropylisocytosine and 6-phenylisocytiosine.*

| entry | band type | 6-isopropylisocytosine | 6-phenylisocytosine |
|---|---|---|---|
| 1 | OH *stretch* | 3333 cm$^{-1}$ | 3374 cm$^{-1}$ |
| 2 | NH/NH$_2$ *stretch* | 3072 cm$^{-1}$ | 3134 cm$^{-1}$ |
| 3 | C=O *stretch* | 1657 cm$^{-1}$ | 1668 cm$^{-1}$ |

Presumably, the amine function of 6-phenylisocytosine is more nucleophilic due to the electron-donating character of the phenyl moiety in comparison with the aliphatic C6-substituted isocytosines.

## 4.3 Microwave heating

Some reaction parameters (*e.g.* temperature or co-solvent) have been changed in a conventionally heated reaction of isocytosines with isocyanates as described in section 4.2. As indicated in chapter 2, comparing time-conversion histories of conventional and microwave heating allows recognition of any possible microwave effect if identical reaction conditions except the method of heating are selected. A quantification of a microwave effect follows from the ratio of the initial reaction rates of both heating methods, see Equation 3.2 in section 3.3. Each figure in this section shows time-conversion histories for both conventional heating (CH) and microwave heating (MW).

**Influence of temperature**
Three experiments were conducted at 74, 85, 100 °C to convert 6-methylisocytosine with an excess of HDI under microwave heating conditions, see Figure 4.6.
For microwave heating initial reaction rates were significantly higher than for oil-bath heating. In the experiments the stirring speed and the temperature were kept as close as possible to those of the oil-bath heated experiments. Intriguingly, the ratio of the initial reaction rates of microwave and conventionally heated experiments increases (higher microwave effect) when the temperature rises (Figure 4.6 (right)).
The relationship in the Arrhenius equation between reaction rate and temperature could give more insight into the fundamental reason for the difference between conventional and microwave heating, the so-called microwave effect.
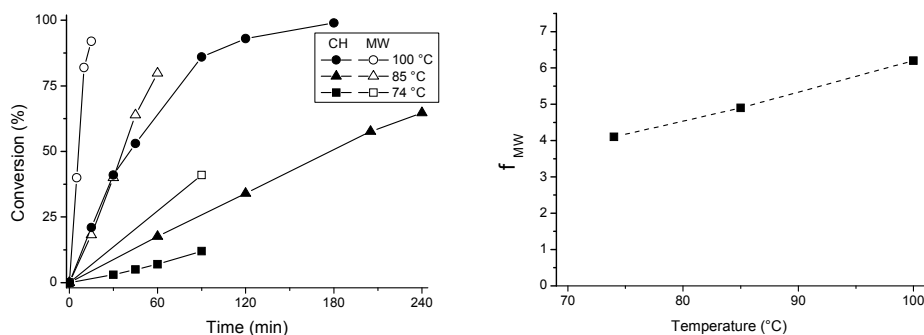
**Figure 4.6**    *(left) Nucleophilic mono-addition of 6-methylisocytosine to hexa-methylenediisocyanate at 74 °C, 85 °C and 100 °C for conventional heating (CH) and microwave heating (MW). (right) Relation between temperature and microwave effect ($f_{MW}$).*

Plotting the initial reaction rate against the reciprocal temperature for experiments with conventional and microwave heating (see Figure 4.7 and Equation 4.1-b) shows that the intercept [ln A'/$C_0$] in the graph differs more than the slope [-$E_a$/R] of both lines.[15] The pre-exponential factor and the apparent activation energy comprises multiple physical parameters, the difference between the pre-exponential factors (*i.e.* ln A'/$C_0$) points out a plausible explanation for the observed rate enhancements.
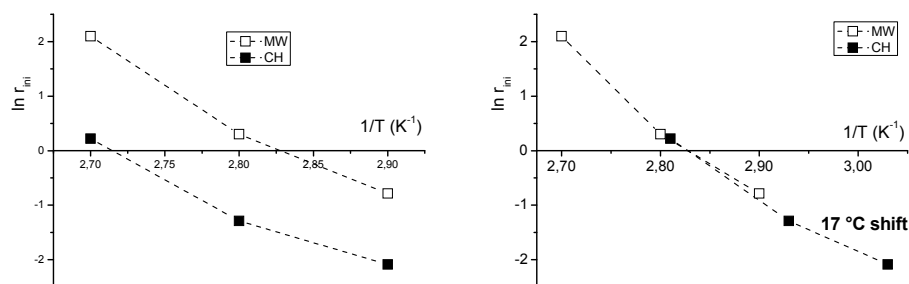


**Figure 4.7**    *(left) Correlation between temperature and initial reaction rate for nucleophilic mono-addition of 6-methylisocytosine and hexamethylene-diisocyanate using conventional and microwave heating. (right) Results of conventional heating shifted with 17 °C to project on microwave heating results.*

The apparent activation energy, consisting of the sum of actual activation energy and heat of solution (chapter 3.2), remains the same under both heating techniques. The pre-exponential factor, although, seems to differ. Thus, this leads to the assumption that limitations in the rate-determining step are less pronounced under microwave irradiation.

**Influence of the co-solvent**
As discussed in section 4.2 the conventionally heated experiments showed that the use of a co-solvent (*e.g.* NMP) resulted in higher reaction rates (Figure 4.3). The results in Figure 4.8 (right) demonstrate that the microwave effect ($f_{MW}$) decreases with increasing weight fraction of NMP. Further addition of NMP to reach a homogeneous solution like in the racemization of *N*-acetyl amino acids (chapter 3) was unrealistic. Replacing 6.5 equivalents of HDI by NMP did not result in a homogeneous reaction mixture. It can be concluded that the addition of a co-solvent leads to a partial dissolution of 6-methylisocytosine and a concomitant vanishing microwave effect.
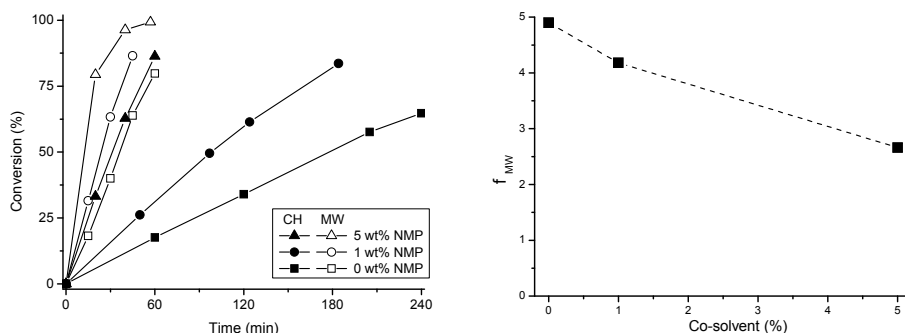


**Figure 4.8**    *(left) Nucleophilic addition of 6-methylisocytosine to hexamethylene diisocyanate at 85 °C for conventional heating (CH) and microwave heating (MW): influence of the weight fraction of co-solvent NMP. (right) Microwave effect as a function of weight fraction of NMP.*

**Scope with various substrates and reagents**
Heterogeneity can be altered, like in the previous section by co-solvent addition, as well as with variation of the reactants. Not only would this expand the scope of microwave-assisted addition of 6-methylisocytosine to hexamethylenediiso-cyanate, but also it might give more insight into the microwave effect.
The differences between both heating techniques are depicted in Figure 4.9 (left) for the mono-additions of 6-methylisocytosine to HDI and HI at 85 °C, showing a $f_{MW}$ for HI of 7.4 and a $f_{MW}$ for HDI of 4.9. A possible explanation for the lower rates

with HI as compared to HDI is the expected poorer solubility of 6-methylisocytosine in HI due to its lower polarity.

Variation of the substituents at the 6-position in the substrate gives also large differences between conventional and microwave heating at 70 °C, see Figure 4.9 (right). The correlation between solubility and reactivity was in general predictable as explained in the previous section of this chapter. However, the correlation between solubility and microwave effect is not completely in line with our expectations (Table 4.4). A better correlation between heterogeneity and microwave effect (*fMW*) for all four substrates can be made when the overall heterogeneity of the reaction mixture is considered for both substrate and product solubility during the conversion (mainly initially). This might explain the high microwave effect for 6-phenylisocytosine in contrast to the absence of a microwave effect for 6-isopropylisocytosine with a similar substrate solubility.

The reactivities of 6-ethyl- and 6-isopropylisocytosine are not significantly different for conventional heating (see Table 4.2). However, with microwave heating only the rate of 6-ethylisocytosine is enhanced. During the reaction of 6-isopropylisocytosine the solubility increases to such a level that no microwave effect could be generated anymore.
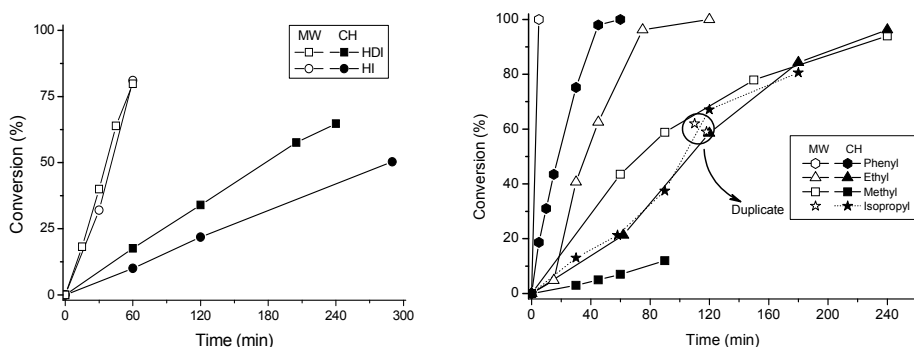


**Figure 4.9**    *(left) Nucleophilic addition of 6-methyl-isocytosine to hexylisocyanate (HI) and hexamethylenediisocyanate (HDI) at 85 °C for conventional heating (CH) and microwave heating (MW). (right) Nucleophilic addition of several 6-substituted isocytosines to hexamethylene-diisocyanate at 70 °C (and for 6-methyl-isocytosine at 74 °C).*

**Table 4.4**    *Outcome of the nucleophilic addition of isocytosine with various substituents at the 6-position to HDI: reactivity with microwave heating and microwave effect.*

| entry | substituent | solubility | reactivity | substituent | microwave effect* | |
|-------|-------------|------------|------------|-------------|-------------------|---|
| 1 | methyl | *low* | *low* | phenyl | *higher* | 8.5 |
| 2 | ethyl | | *medium* | methyl | | 5.4 |
| 3 | isopropyl | | *low* | ethyl | | 2.8 |
| 4 | phenyl | *higher* | *higher* | isopropyl | *low* | *nil* |

\* *f_{MW} at 70 °C (and for 6-methylisocytosine at 74 °C)*

## 4.4 Discussion & conclusion

All the reactions discussed were faster (or in case of 6-isopropylisocytosine identical) when microwave heating was employed. Reducing the heterogeneity diminished the microwave effect in a similar way as described in chapter 3 for the racemization of *N*-acetyl amino acids. Solubility of the substrate is an important factor, albeit that the overall heterogeneity (considering substrate *and* product) allows perhaps a better prediction of a positive microwave effect for certain reaction systems.

**Microwave effect**
The results of our research demonstrate that no microwave effects occur for homogeneous reactions, see chapter 3. Heterogeneity alone was not sufficient to induce a microwave effect. So far a positive microwave effect was only observed in solid-liquid systems with very low solubilities of the solid reactants (and not of the reagents) involving relatively fast reactions in the diffusion layer. It is exactly in these diffusion layers where selective heating can occur.
In the case of the addition of 6-methylisocytosine to hexamethylene diisocyanate, 6-methylisocytosine slightly dissolves which results in an absorption enhancement of microwave irradiation. In addition, temperature locally increases leading to an even higher solubility and reaction rate till a local thermal equilibrium is obtained.

The occurrence of such a microwave effect at the interphase was also demonstrated before through modeling a chemical conversion with microwave heating.[16-18]
In our cases neither the solid nor the solvent were good microwave absorbers, which was demonstrated by simple heating experiments.
Yet these effects can not locally be measured by any sensor, but its effect is indirectly witnessed by higher reaction rates and higher pre-exponential factor considerations. Figure 4.6 (left) illustrates an example representing a conversion of

6-methylisocytosine for the conventionally heated experiment at 100 °C almost similar to the microwave-heated reaction at 85 °C. If the reaction predominantly takes place in the diffusion layer then this layer conclusively has an average temperature of 100 °C, but the bulk temperature is measured to be 15 °C lower. Again, a value close to 17 °C derived from pre-exponential factor considerations in section 4.3.

Improvement of stirring has an effect on the thickness of the diffusion layer, nevertheless did not lead to a vanishing microwave effect in our cases. In contrast to the racemization process as described in chapter 3 a homogeneous solution could not be obtained and, therefore, a diffusion layer always remained present. Consequently, a similar microwave effect is still observed.

## 4.5 Remark

*Shifting point of view: microwave effect.* *Electromagnetic acoustic transducers (EMAT) are devices which generate electromagnetic pulses. At each boundary or defect an acoustic wave is formed. By reflection the specimen reveals its inner structure. This method is generally used to test metal objects. The creation of an electromagnetic pulse allows formation of an acoustic or an ultrasonic wave at boundary layers.*

*This phenomenon is also the reason why humans or animals exposed to electromagnetic waves hear "clicks". A thermal elastic wave is produced and it travels to the inner ear, where a sound is heard. The thermal expansion in this case is small, but very fast.*

*Two specialists (Hosten (Bordeaux, France)[19] and Lin (Illinois, Chicago, USA))[20] in this field have not excluded the existence of the transformation of electromagnetic waves to ultrasonic or acoustic waves in our heterogeneous reaction systems. Although EMAT technology is used at another scale and energies are higher in power, the generation of local ultrasonic waves may have a positive influence on the reaction rate of solid-liquid reactions.[21] Cavitation at the interface of solid / liquid can locally stimulate mass transport or temperatures. The application of ultrasonic waves is a generally accepted alternative-energy source to activate a specific reaction (e.g. Grignard reagent formation), also known as sonochemistry.*

## 4.6 Experimental section

*All microwave-heated experiments were performed in a MicroSynth of Milestone srl., Italy with internal fibre-optic temperature measurement. For other details, see the experimental section of chapter 2. During reaction aliquots were taken and quenched in cold MTBE (2 mL, 0°C). The suspension was filtered and washed twice with cold MTBE (0.5 mL). The remaining solid was dried under reduced pressure at 40 °C and analyzed by $^1$H-NMR (conversion based on ratio isocytosine and product).*

**Nucleophilic additions:**

***N-(6-Isocyanatohexyl)-N'-(6-methyl-4-oxo-1,4-dihydropyrimidin-2-yl)urea (4)****: A 20-mL reaction tube was charged with 6-methylisocytosine[2] (0.75g, 6.0 mmol) and hexane-1,6-diisocyanate (7.5 g, 44.6 mmol). The tube was flushed with argon and closed. Temperature was measured via an insert. The reaction mixture was heated at 85 °C with stirring for 2 h in the microwave oven (average power: 25 W / max: 200 W). Thereafter, the mixture was diluted with MTBE (15 mL), and after cooling the suspension was filtered and washed twice with MTBE (1.5 mL). The remaining solid was dried under reduced pressure at 40 °C and analyzed. Yield after work-up: 1.39 g (79%); $^1$H-NMR (400 MHz) in CDCl$_3$/d-TFA (1/1 vol %) δ 6.3 (s, 1H, CH=C-CH$_3$), 3.3 (t, 2H, NH-C**H$_2$**, 3.2 (t, 2H, C**H$_2$**-NCO), 2.5 (s, 3H, C**H$_3$**-C=CH), 1.8 (m, 2H, NH-CH$_2$-CH$_2$), 1.6 (m, 2H, C**H$_2$**-CH$_2$-NCO), 1.5 (m, 4H, (C**H$_2$**)$_2$-(CH$_2$)$_2$-NCO). Conventionally heated experiment (4h). Yield after work-up: 1.55 g (88 %) mono-substituted product.*

***N-(6-Isocyanatohexyl)-N'-(6-ethyl-4-oxo-1,4-dihydropyrimidin-2-yl)urea****: A 20-mL reaction tube was charged with 6-ethylisocytosine[11] (0.84g, 6.0 mmol) and hexane-1,6-diisocyanate (7.5 g, 44.6 mmol). The tube was flushed with argon and closed. Temperature was measured via an insert. The reaction mixture was heated at 85 °C with stirring for 2 h in the microwave oven (average power: 25 W / max: 200 W). Thereafter, the mixture was diluted with MTBE (15 mL), and after cooling the suspension was filtered and washed twice with MTBE (1.5 mL). The remaining solid was dried under reduced pressure at 40 °C and analyzed. $^1$H-NMR (400 MHz) in CDCl$_3$/d-TFA (1/1 vol %) δ 6.4 (s, 1H, C**H**=C-C$_3$H$_7$), 3.4 (m, 2H, NH-C**H$_2$**, 3.2 (m, 2H, C**H$_2$**-NCO), 2.8 (q, 2H, C**H$_2$**-C=CH), 1.8 (m, 2H, NH-CH$_2$-CH$_2$), 1.7 (m, 2H, C**H$_2$**-CH$_2$-NCO), 1.5 (m, 4H, (C**H$_2$**)$_2$-(CH$_2$)$_2$-NCO), 1.4 (t, 3H, C**H$_3$**-CH$_2$-C=CH). Yield: 70 %.*

***N-(6-Isocyanatohexyl)-N'-(6-isopropyl-4-oxo-1,4-dihydropyrimidin-2-yl)urea***: *A 20-mL reaction tube was charged with 6-isopropylisocytosine[11] (0.92g, 6.0 mmol) and hexane-1,6-diisocyanate (7.5 g, 44.6 mmol). The tube was flushed with argon and closed. Temperature was measured via an insert. The reaction mixture was heated at 85 °C with stirring for 2 h in the microwave oven (average power: 24 W / max: 70 W). Thereafter, the mixture was diluted with MTBE (15 mL), and after cooling the suspension was filtered and washed twice with MTBE (1.5 mL). The remaining solid was dried under reduced pressure at 40 °C and analyzed. $^1$H-NMR (400 MHz) in $CDCl_3$/d-TFA (1/1 vol %) δ 6.4 (s, 1H, CH=C-CH$_3$), 3.3 (t, 2H, NH-CH$_2$, 3.2 (t, 2H, CH$_2$-NCO), 3.0 (m, 1H, C$_2$H$_6$-CH -C=CH), 1.8 (m, 2H, NH-CH$_2$-CH$_2$), 1.6 (m, 2H, CH$_2$-CH$_2$-NCO), 1.4 (m, 4H, (CH$_2$)$_2$-(CH$_2$)$_2$-NCO, 1.3 (d, 6H, C$_2$H$_6$-CH-C=CH).Yield: 63 %.*

***N-(6-isocyanatohexyl)-N'-(6-phenyl-4-oxo-1,4-dihydropyrimidin-2-yl)urea***: *A 20-mL reaction tube was charged with 6-phenylisocytosine[11] (1.12g, 6.0 mmol) and hexane-1,6-diisocyanate (7.5 g, 44.6 mmol). The tube was flushed with argon and closed. Temperature was measured via an insert. The reaction mixture was heated at 85 °C with stirring for 2 h in the microwave oven (average power: 22 W / max: 120 W). Thereafter, the mixture was diluted with MTBE (15 mL), and after cooling the suspension was filtered and washed twice with MTBE (1.5 mL). The remaining solid was dried under reduced pressure at 40 °C and analyzed. $^1$H-NMR (400 MHz) in $CDCl_3$/d-TFA (1/1 vol %) δ 7.6-7.8 (m, 5H, C$_6$H$_5$-C=CH), 6.8 (s, 1H, CH=C-CH$_3$), 3.4 (t, 2H, NH-CH$_2$, 3.2 (t, 2H, CH$_2$-NCO), 1.8 (m, 2H, NH-CH$_2$-CH$_2$), 1.7 (m, 2H, CH$_2$-CH$_2$-NCO), 1.5 (m, 4H, (CH$_2$)$_2$-(CH$_2$)$_2$-NCO). Yield: 83 %.*

***N-hexyl-N'-(6-methyl-4-oxo-1,4-dihydropyrimidin-2-yl)urea (5).*** *A 20-mL reaction tube was charged with 6-methylisocytosine (0.75g, 6.0 mmol) and hexylisocyanate (5.67 g, 44.6 mmol). The tube was flushed with argon and closed. Temperature was measured via an insert. The reaction mixture was heated at 85 °C with stirring for 4 h in a Milestone microwave oven (average power: 25 W / max: 200 W). Thereafter, the mixture was diluted with MTBE (15 mL), and after cooling the suspension was filtered and washed with MTBE (1.5 mL). The remaining solid was dried under reduced pressure at 40 °C and analyzed by $^1$H-NMR (400 MHz) in $CDCl_3$/d-TFA (1/1 vol %) δ 6.3 (s, 1H, CH=C-CH$_3$), 3.3 (t, 2H, NH-CH$_2$, 2.5 (s, 3H, CH$_3$-C=CH), 1.8 (m, 2H, NH-CH$_2$-CH$_2$), 1.5 (m, 6H, (CH$_2$)$_4$-(CH$_2$)$_2$-NH), 1.4 (t, 3H, CH$_2$-CH$_3$). Yield: 73 %.*

**Typical procedure for all oil-bath heated reactions:**
*The same procedure was executed for the oil-bath experiment substituting microwave with oil-bath heating, except the duration of the reaction might be prolonged.*

**N,N'-dihexylurea (6).** *A 20-mL reaction tube was charged with n-hexylamine (234 mg, 2.31 mmol), toluene (5 mL) and hexylisocyanate (280 mg, 2.2 mmol). The reaction mixture was refluxed for 2 h. Thereafter, the solvent was removed at 50 °C under reduced pressure. $^1$H-NMR (300 MHz) in CDCl$_3$ δ 4.3 (s, 1H, NH-CO), 3.2 (t, 2H, CH$_2$-NH), 1.5 (m, 2H, CH$_2$-CH$_2$-NH), 1.3 (m, 6H, (CH$_2$)$_3$-CH$_3$), 0.9 (t, 3H, -CH$_3$). GC-MS (m/z):228 (FW 228).*

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# Chapter 5

# 5

# Continuous-flow reactor; aspects of design

# Abstract

The best opportunities to scaling-up microwave-assisted chemistry lie in continuous operation or in flow processing.

An effective transformation of organic reactions from batch to continuous operation is only suited for fast reactions. The introduction of a loop expands the scope of the continuous-flow reactor.

Microwave heating is more expensive in the acquisition and in its energy consumption. However, efficiency grows as the loss tangent or the scale increases. Nonetheless on an industrial scale, steam heating stays more beneficial when other criteria, such as safety, are less decisive.

The development of a fume hood concept allows having a large degree of flexibility over process research, with the option to produce a considerable amount of product. Further scaling out of the fume hood concept is expected to be fast and straightforward with parallel units, if the costs are acceptable within the process' budget.

Although the technology is available to scaling-up processes under microwave-heating conditions, the sum of all process criteria shows whether it is a preferred method of operation.

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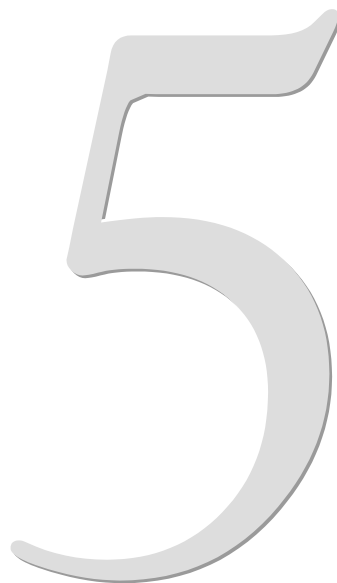
## 5.1 Introduction

In recent years much effort has been invested in an increasingly competitive world to meet the requirements of the fine chemical and pharmaceutical industry with respect to "first-time-right" performance, a short-time-to-market and avoiding surprises during process scale-up. A demand for larger quantities is not just rewriting a recipe by replacing "mg" with "kg" during chemical process research.

Process intensification based on *e.g.* microreactor technology and microwave heating, as relatively novel tools in the field of organic chemistry, is actively pursued to achieve a better position in the industrial scene. Introduction of these novel techniques in the field of organic chemistry expands the toolbox of today's chemists. Increase of reaction rates and improved selectivity, combined with the automation of repetitive procedures, demonstrate the advantageous application of these enabling techniques and are considered to be suitable to improve this position in the industrial scene. One of the major weaknesses of microwave-assisted chemistry is scaling-up. Since the penetration depth of microwaves is limited, the best chances for increased production volumes lie in relatively small-scale continuous operations, somewhat uncommon in the fine chemical industry.[1-3]

In the first two sections microwave heating is discussed in terms of application in continuous operations and in a loop reactor operated batchwise. Then microwave irradiation is considered as a potentially efficient heating source. Subsequently, the tubular reactor - part of our Milestone FlowSynth equipment - is discussed to characterize and to model the reactor with respect to standardized equipment. Ultimately, the performance of the FlowSynth is illustrated in the fume hood concept.

## 5.2 Continuous-flow reactor

In a chemical laboratory most reactions are carried out batchwise. Large-scale production like in the field of bulk chemicals prefers, however, continuous operation. Batch and continuous operation evidently have their advantages and disadvantages, but with the introduction of microreactors flow chemistry will be selected in view of achieving constant product quality over time, as well as improved selectivity, heat transfer and safety. A typical diameter in microreactors is below 1 mm.[4] Consequently, the volume-to-surface ratio makes these reactors ideal heat exchangers. A combination with microwave heating enables quick heating and cooling of the process streams. Handling of solids, however, is a key

problem to overcome when microreactors are used. With solid/liquid systems there is a risk of plugging. For catalytic reactors the plugging by catalyst particles can be overcome by catalyst-containing coatings or a fixed bed. Increasing the diameter of the tubing above 1 mm opens up a window for heterogeneous reactions, especially solid/liquid systems.

As mentioned before the penetration depth ($\delta_P$) of microwaves is limited in the range of centimeters depending on the composition and physical properties of the reaction mixture. The penetration depth is expressed in the distance where the energy is reduced to 37 % (see Equation 5.1).[5] Therefore, the reactor diameter for microwave heating equipment ranges between 5 to 100 mm.[6]

Based on the specification of the reaction conditions, selection of reactor type and peripheral equipment (for example type of pump) has to be made. So far in our case only one type of microwave equipment is commercially available involving a combination of a membrane pump, a tubular reactor and a microwave oven; all controlled by one computer. This setup is known as FlowSynth of Milestone srl, Italy (Figure 5.1 (left)).[7,8] The pre-commercial version of the FlowSynth is described by the group of Ondruschka.[9] This novelty has been patented.[10,11]

$$\delta_p = \frac{\lambda_0 \sqrt{\varepsilon'}}{2\pi\varepsilon''} \qquad (5.1)$$

$\delta_p$ = penetration depth [m]

$\lambda_0$ = free space wavelength [m]

$\varepsilon'$ = dielectric constant

$\varepsilon''$ = dielectric loss
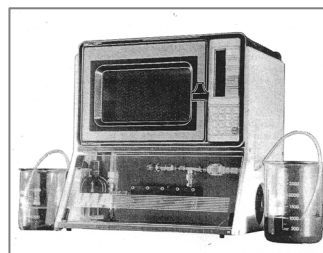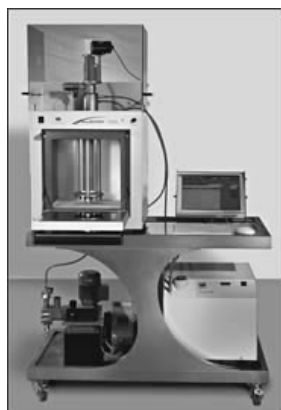


**Figure 5.1**  *(left) FlowSynth of Milestone srl, Italy. (right) Continuous-flow reactor from the group of Strauss.[20]*

**Flow chemistry**

Most studies with continuous-flow reactors are reported in the field of organic chemistry and describe the application of conventional heating; so-called flow chemistry.[11-14]

Today's flow chemistry is based on the principle of Merrifield's solid-phase peptide synthesis.[14-16] Solid-phase chemistry itself is specifically used under flow conditions[11] and this type of work has been extensively studied and promoted by, for example, Ley and Baxendale.[18,19]

Initial research in flow chemistry by microwave heating was done by Strauss and co-workers. Figure 5.1 (right) shows the equipment used. The first publication from the group of Strauss appeared in 1992 with positive expectations of this novel reactor design for the future.[20-23] The combination of microwave heating and flow chemistry has also been investigated by groups which had their expertise primarily in either microwave technology or flow chemistry.[1,9,24-29] Attempts to scale-up flow chemistry mostly involve either homogeneous reactions or heterogeneous reactions by means of immobilized reagents / catalysts.[30-33] There is, to the best of the our knowledge, only one small-scale example of an inorganic solid-liquid flow system.[34]

The use of continuously operated reactors demands for relatively fast reactions, otherwise flow rates have to become extremely low or reactors become too large.[35] Residence time is the key parameter determining the degree of conversion. One way to combine a high flow rate with complete conversion is to completely recycle the outlet, resulting in a batch-loop reactor. In this way, the advantages of a tubular reactor and a batch reactor are combined.

## 5.3 Batch-loop reactor

Roughly, the setup of a batch-loop reactor that we have used, see Figure 5.3 (left), involves flow chemistry in a microwave oven. This approach is basically an ideal situation to accommodate reactions requiring different residence times, to transfer a small-scale batch reaction into a flow setup and to increase the productivity by means of parallel circuits (*i.e.* scaling out).

So far to the best of our knowledge, only one fine chemical reaction on industrial scale is reported, which is similar to our approach. The process includes esterification of (*S*)-pyroglutamic acid in the production of a cosmetic product, Laurydone (section 2.6, Figure 5.2). The Laurydone case as an one-in-a-kind example attracted our attention and as a consequence the concept of the continuous-flow reactor was elaborated, see Chapter 6.
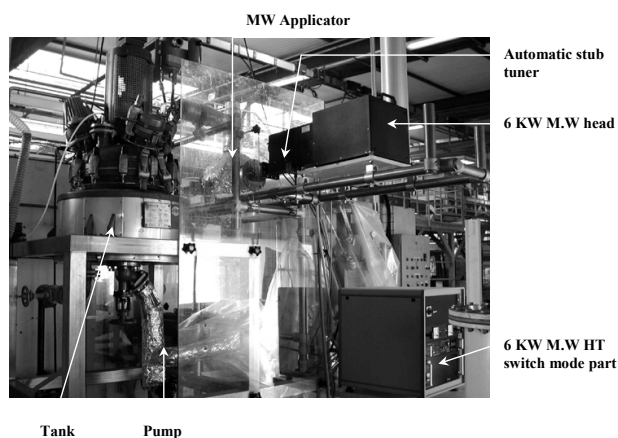
**Figure 5.2**    *Picture of the batch-loop reactor in the Laurydone process. On the left part of this picture the tank is situated with a recycle loop including pump. In the middle section a safety screen is positioned and the right part depicts on the bottom a MW control unit on top of that the MW generator and adjacent the MW applicator. The recycle loop is partly situated in the MW applicator [reference 36].*

Our process design is predominantly based on the FlowSynth, which was commercially provided by Milestone srl (Figure 5.1 (left) and Figure 5.4).

The reactants are preferably pre-mixed in a vessel. In another small vessel pure solvent is stored on behalf of start-up and shutting-down procedures. With a series of ball valves it is possible to switch between several flow profiles including one to clean the reactor coil in a reverse flow. All the liquids or slurries are transported either by a membrane pump or by a gear pump. The pump forces the reaction mixture into the microwave-heated reactor. Inside this tubular reactor mixing is possible. On top of the reactor a cooling unit is placed. The cooler is manually controlled in temperature, but it can be switched on/off by the computer. At the outlet initially a backpressure valve has been installed to control the pressure till 30 bars. Two sensors monitor on-line the temperature in the upper part of the reactor coil and at the final outlet. The pressure is monitored at the outlet of the pump. Besides these parameters the stirrer speed, pump speed and the microwave power are registered by the software program.

The tubing has been thermally insulated to prevent drastic temperature drops, which largely influence the solubility of the reactants. Plugging in these channels or in the valves is one of the key issues in this setup. In principle the loop reactor can be operated as a closed-loop system or in a continuous mode. The continuous

mode will be similar to one or a series of continuous stirred tank reactors (CSTR's). In the batch-loop as well as in the continuous mode a feed point can be incorporated in the loop. Feeds of gases and liquids are then rapidly dispersed in the circulating liquid. Consequently, the reaction rates are improved provided reaction rates are controlled by mass transfer between the phases. A typical example is the Buss reactor applied for hydrogenations, see Figure 5.3 (right).[37]
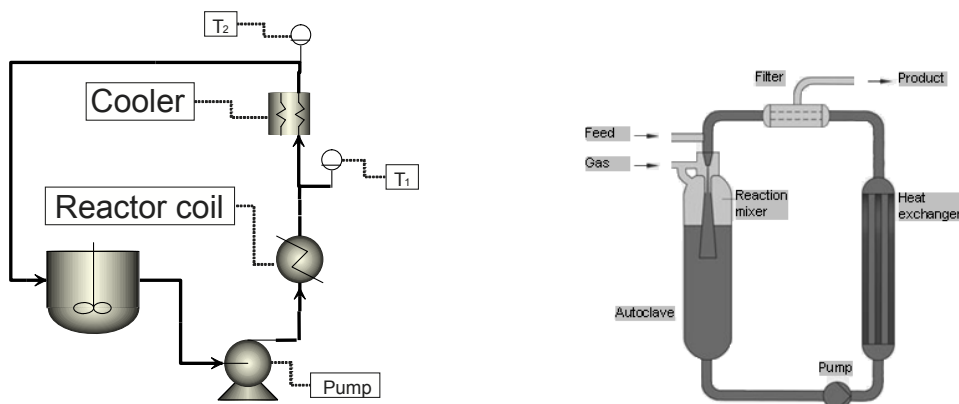


**Figure 5.3** *(left) Batch-loop reactor and components. (right) Buss® loop reactor from Buss ChemTech AG, Switzerland.*

Based on the results and the experience gained in the processes discussed in chapter 6 (*e.g.* biocatalysis or racemization), the FlowSynth reactor has been adapted at various places to enable processing of heterogeneous reactions. Our modifications are marked with circles in Figure 5.4.
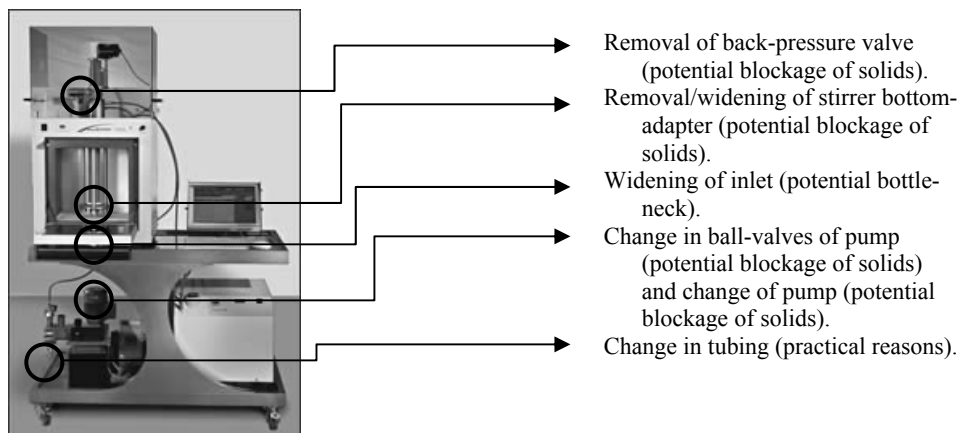


**Figure 5.4** *Various modifications of the original FlowSynth apparatus.*

## 5.4 Energy balance

The chemical conversion is one of the key performance parameters to compare conventional with microwave heating on lab scale. To make microwave heating feasible on a larger scale this technique should perform better than conventional heating procedures. Besides productivity, selectivity and safety also the investment costs of the hardware play a role. The investments to incorporate a microwave-heated setup should be at least comparable to that of traditional equipment and utilities in the fine chemical industry (*e.g.* heating with condensing steam). Any supplementary costs have to be compensated by the added value of improved reaction conditions (*e.g.* microwave effect) or more effective down-stream processing. Apart from these direct economic considerations also the energy consumption is a point of interest when microwave heating is compared with conventional heating techniques.

Microwave heating technology is draped with gold considering all positive claims regarding chemical conversions or selectivity. So, high expectations are ascribed to microwave technology in the future.[38-40]
The starting point needs to be identical, being gas as a natural source of energy, to make a fair comparison between energy efficiencies of conventional and microwave heating. Figure 5.5 illustrates the energy efficiency for each transformation step.
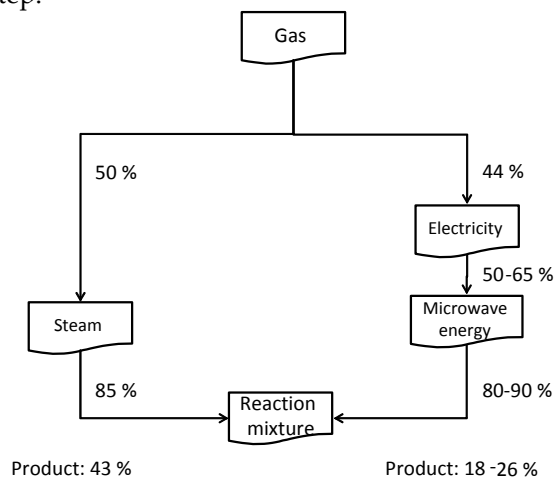


**Figure 5.5**    *Energy-efficiency of conventional heating (steam) and microwave heating.[41-43]*

Different energy sources (gas or electricity) include different prices, based on the technology necessary to generate this power.[41-44] In short, microwave heating loses at least a factor of 2 (43 % over 22 %, Figure 5.4) times more energy in its fore track and at the end the energy bill is minimal a factor of 8 (0.088 € over 0.011 €)[44] higher compared to steam heating for industrial applications. Altogether, the energy costs will be higher for microwave heating.

Note that, highly dedicated equipment tuned to a specific process can reach the highest efficiencies compared to a single process in a multi-purpose plant. Nevertheless, if microwave heating can be applied to processes with high degrees of selective heating (drying), this technique might even have a better heat efficiency as compared to conventional heating.

The efficiency values given in Figure 5.5 are based on different literature sources and experimental results.[41-44] The efficiency of the transition from microwave energy to the reaction mixtures is the most fluctuating value depending on scale, equipment type and the loss tangent. Hoogenboom *et al* reported that the losses on small scale are much higher compared to larger scales.[45] Predominantly this is due to heat losses to the environment, based on a high surface-to-volume ratio for small equipment. Thermal insulation of the reaction vessel with microwave-transparent material is a simple solution to increase the energy efficiency. Fortunately, a low heat conductivity is also a good material property of polymer materials such as Teflon and PEEK (poly-ether-ether-ketone) which are commonly used to construct microwave-heated reactors with a high chemical resistance or high mechanical strength (*e.g.* for pressure), respectively.

A more detailed overview of the efficiencies of microwave energy into heat for three solvents under different conditions is depicted in Tables 5.4 (for *p*-xylene), 5.5 (for demi-water) and 5.6 (for ethylene glycol) in section 5.8. The efficiency was calculated by the ratio of the thermal energy required to heat up the solvent (see Equation 5.2) and the amount of electromagnetic energy delivered by the microwave oven.

$$\eta = \frac{\phi_m \cdot c_p \cdot \left(\Delta T\right)_{observed}}{\text{microwave power used}} \tag{5.2}$$

$\phi_m$ = mass flow rate $[\text{kg} \cdot \text{s}^{-1}]$

$c_p$ = heat capacity $[J \cdot kg^{-1} \cdot K^{-1}]$

$\Delta T$ = difference in temperature, outlet - inlet $[K]$

$\eta$ = efficiency [%]

Experiments were performed with the FlowSynth equipped with a typical stirrer shown in Figure 5.6.
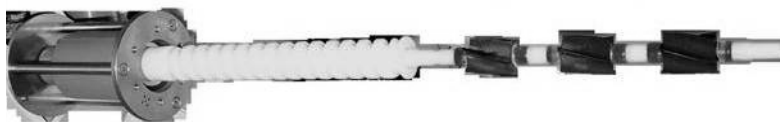


**Figure 5.6**    *Stirring shaft with three Weflon blades for the tubular reactor of the FlowSynth.*

The experimental results demonstrate that the absorption of microwaves increases in the order of *p*-xylene < demi-water < ethylene glycol. This could be expected from the following literature data; loss tangents for ethylene glycol, demi-water and *p*-xylene at 20 °C are 1.35; 0.127 and 0.0011, respectively.[‡] Operating in a turbulent flow regime (see section on *Flow and mixing*) improves the efficiency. Each solvent appears to have an average maximum, which is not influenced by the operational conditions. The error margin of these measured values is in the range of 5-10 %.

Besides energy efficiency, safety issues can be decisive in selecting the method of operation. As an example, a case study on hydrogen cyanide production made by DuPont illustrates the advantages of microwave heating in the processing of hazardous chemicals.[46] Here hydrogen cyanide is synthesized using a platinium catalyst at temperatures over 1000 °C. The advantage of microwave energy is selective heating and the possibility of an immediate interruption of heating. However, ten years ago a lack of availability of technology and the high operating costs made DuPont to decide to go for the conventional way. Nevertheless, DuPont patented the advanced technology.[47]

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[‡] physical constants are obtained from Handbook of Chemistry and Physics; 89th Edition; **2008-2009** (online edition, Lide, D. R.)

## 5.5 Experimental characterization

Characterization of the flow reactor and its properties is necessary to compare it with standardized equipment. This will also clarify the limitations of the flow reactor used and allows definition of an operational window.

**Reactor type**
At first sight the reactor coil in the FlowSynth looks like a tubular reactor and the presence of stirrers (Figure 5.6) may induce (additional) residence time distribution. Measurement of the residence-time distribution (RTD) makes it possible to characterize the reactor more specifically.[48]

The theory of RTD was first proposed by MacMullin and Weber[49], and worked out in more relevance by Danckwerts[50] some years later. A tracer is injected in the feed to the reactor. Detection of the tracer is performed at the outlet. A pulse or a step injection can be chosen to introduce the tracer. In our setup the response on a tracer pulse has been measured. These measurements give access to the exit-age function $E(t)$ is the RTD function. $E(t)$ quantifies the time-dependent fraction of the tracer. Equation 5.3-a shows how $E(t)$ can be calculated from the response. The velocity ($v$) is constant, the concentration $C(t)$ of the tracer is measured and the exact amount of tracer ($N_0$) is not directly known. $E(t)dt$ stands for the fraction tracer leaving the system between $t$ and $t + dt$. Note that for $t \rightarrow \infty$ all the tracer should have left the reactor, see Equation 5.3-b.

$$E(t) = \frac{v.C(t)}{N_0} = \frac{C(t)}{\int_0^\infty C(t).dt} \qquad \textbf{(5.3-a)} \qquad \int_0^\infty E(t)dt = 1 \qquad \textbf{(5.3-b)}$$

Benzyl alcohol, as tracer in a stream of toluene, has been measured by GC-FID. In this way there is a linear relation between the measured GC-peak area and the actual concentration ($C(t)$). The exit-age function $E(t)$ is used in a one-parameter model for non-ideal reactors implying the number of equally sized CSTR's in series which gives the same $E(t)$ as for the reactor considered. The only parameter is the number of tanks, n, in this series and it is expressed as given in Equations 5.4.
The number of tanks (n) is calculated from the dimensionless variance. The variance itself is the square of the standard deviation ($\sigma$) and the mean residence time is $\langle \tau \rangle$. [48]

$$\langle\tau\rangle = \int_{0}^{\infty} t \cdot E(t)dt \qquad \text{(5.4-a)}$$

$$E(t) = \frac{n^n \cdot t^{n-1} \cdot e^{-\frac{n \cdot t}{\langle\tau\rangle}}}{\langle\tau\rangle^n \cdot (n-1)!} \qquad \text{(5.4-b)}$$

$$\sigma^2 = \int_{0}^{\infty} \left(t - \langle\tau\rangle\right)^2 \cdot E(t)dt$$

$$n = \frac{\langle\tau\rangle^2}{\sigma^2}$$

The RTD results are influenced when the reactor setup is operated under different conditions. The relationship between the number of equally sized tanks in series and the variation of flow and stirrer speed are summarized in Table 5.7, section 5.8. On average the FlowSynth is equivalent with approximately three equally sized CSTR's in series. If the flow inside the reactor is in synchronization with the stirrer speed then an optimum can be observed. This indicates that the stirred tubular reactor tends to perform more like a plug-flow reactor. Any disturbance leads to more axial mixing, which has the tendency to be more equivalent to a continuous stirred tank reactor (CSTR). The presence of a shoulder or split-peak is a sign for two or multiple routes which lead to differences in the residence time (see Figure 5.9 (left) in section 5.8). Figure 5.9 (right) in section 5.8 illustrates the theoretical distribution for a number of CSTR's in series.

**Flow and mixing**
The Reynolds number, as a dimensionless number, represents the ratio of inertia forces and viscous forces. The Reynolds number characterizes in this way the flow regime of the experimental conditions.
Mixing can be crucial, not only to bring the reactants together (mass transfer), but also to remove/supply the heat for temperature control during the reaction (heat transfer). For mass as well as for heat transfer the reaction rate is influenced by the degree of mixing. Table 5.1 gives an overview of the length scales of concentration leveling and time constants of reaction.[51]

**Table 5.1** *Mixing regimes related to reaction time constants[51]*

| entry | time constant ($t_{reaction}$) | type of mixing | |
|---|---|---|---|
| 1 | 10 min-hrs | independent of mixing (intrinsic kinetics) | |
| 2 | sec-min | macromixing[*] | (*i.e.* circulation) |
| 3 | ms | micromixing[*] | (*i.e.* diffusion) |

* *These names reflect the different length and time scales of the dominating mechanism.*

The tubing and the reactor have different diameters. Depending on the flow rate a certain reaction mixture or solvent has a laminar or turbulent pattern. If the Reynolds number (Re) is over 3500 the flow will be turbulent in a tube, see Equation 5.5-a. In case of a turbulent flow the heat exchange from the Weflon blades of the semi coil-shaped stirrer inside the reactor column towards the reaction mixture is much more efficient. Table 5.2 gives an overview of the conditions to convert a laminar flow in the reactor (without stirring) into a turbulent regime. The influence of stirring on the Reynolds number is summarized in Table 5.3 using equation 5.5-b.

$$\text{Re}_{tube} = \frac{d_t \cdot u \cdot \rho}{\mu} \qquad \textbf{(5.5-a)} \qquad \text{Re}_{imp} = \frac{\rho \cdot N \cdot d_{imp}^2}{\mu} \qquad \textbf{(5.5-b)}$$

$d_t$ = tube diameter [m]

u = mean velocity $[m \cdot s^{-1}]$

$\rho$ = density $[kg \cdot m^{-3}]$

$\mu$ = dynamic viscosity $[Pa \cdot s]$

$d_{imp}$ = impeller diameter [m]

N = impeller speed $[s^{-1}]$

$\rho$ = density $[kg \cdot m^{-3}]$

$\mu$ = dynamic viscosity $[Pa \cdot s]$

**Table 5.2**  *Relationship between flow rate and Reynolds number\* in the reactor coil at four temperatures.*

| temperature (°C) | flow rate (mL.min$^{-1}$) | | | | |
|---|---|---|---|---|---|
| | 53 | 115 | 167 | 214 | 250 |
| 25 | 31 | 69 | 100 | 128 | 149 |
| 50 | 40 | 89 | 128 | 165 | 192 |
| 75 | 50 | 110 | 158 | 204 | 238 |
| 100 | 60 | 132 | 191 | 245 | 286 |

\* *Re using Equation 5.5-a; $d_t$= 1.75·10$^{-2}$ m.*

**Table 5.3**  *Relationship of stirring speed and Reynolds number\* in the reactor coil at four temperatures.*

| temperature (°C) | stirrer speed (rpm) | | | | |
|---|---|---|---|---|---|
| | 60 | 195 | 322 | 380 | 425 |
| 25 | 402 | 1306 | 2191 | 2546 | 2854 |
| 50 | 517 | 1680 | 2817 | 3273 | 3669 |
| 75 | 640 | 2080 | 3488 | 4054 | 4544 |
| 100 | 769 | 2501 | 4193 | 4873 | 5463 |

\* *Re using Equation 5.5-b; $d_{imp}$= 1.68·10$^{-2}$ m.*

**Heat transfer**

The Nusselt number (Nu) is the ratio of the convective heat transfer and the conductive heat transfer. Equations 5.6 and 5.7 give the definition of the Nusselt number and an empirical dimensionless correlation from heat transfer in stirred tanks, respectively.[52] The heat flow rate from the Weflon blades ($\phi_q$) to the fluid in the reactor is estimated by Equation 5.8. Solvents with a low loss tangent can only absorb microwave energy indirectly via the Weflon blades located at the stirrer shaft in the tubular reactor. Efficient heat transport prevents high temperatures of the heating surface (A = 95 cm²) of the Weflon blades (Equation 5.8). With the assumption of direct and fast absorption of microwaves by the Weflon blades the temperature is at a constant value.

In case of *p*-xylene ($\lambda$ = 0.124 W.m⁻¹.K⁻¹) and a relatively low stirrer constant ($c_r$ = 0.36; blade stirrer, no baffles)[52] the Nusselt number will range from 100 to 200 depending on temperature (50 – 100 °C) and stirrer speed (200 - 400 rpm). The heat transfer coefficient (h), consequently, is calculated to range from 367 till 725 W.m⁻².K⁻¹. Typically the surface of the blades can reach a temperature of 160 °C when an incoming stream of *p*-xylene at room temperature is heated up to 120 °C for an efficient microwave-induced power input of 277 W into the solvent.

$$\langle Nu \rangle = c_r \cdot \mathrm{Re}^{2/3} \cdot \mathrm{Pr}^{1/3} \cdot V_i^{0.14} \qquad \textbf{(5.6)}$$

$$\langle Nu \rangle = \frac{\langle h \rangle \cdot L}{\lambda} \qquad \textbf{(5.7)}$$

$\langle \mathrm{Nu} \rangle$ = Nusselt number
$c_r$ = stirrer constant
Re = Reynolds number
Pr = Prandtl number
$V_i$ = viscosity constant ( $\approx 1$)

$\langle \mathrm{Nu} \rangle$ = Nusselt number
$\langle h \rangle$ = heat transfer coefficient
L = characteristic length
$\lambda$ = thermal conductivity

$$\phi_q = \langle h \rangle \cdot A \cdot (\Delta T)_{\ln} \qquad \textbf{(5.8)}$$

$\phi_q$ = heat supplied to the system $[J \cdot s^{-1}]$
$\langle h \rangle$ = overall heat transfer coefficient $[J \cdot s^{-1} m^{-2} \cdot K^{-1}]$
A = surface $[m^2]$
$(\Delta T)_{\ln}$ = logarithmic average temperature difference [K]

$$(\Delta T)_{\ln} = \frac{\left(T_{out} - T_{blade}\right) - \left(T_{in} - T_{blade}\right)}{\ln\left(\frac{T_{out} - T_{blade}}{T_{in} - T_{blade}}\right)}$$

*Physical constants are obtained from Handbook of Chemistry and Physics; 89th Ed.; **2008-2009** (online ed., Lide, D. R.); $V_i$ is ratio of the viscosities at $T_{bulk}$ and $T_{bl}$, which are equal.*

## 5.6 Integration to a fume hood concept

In fine chemicals manufacturing the reaction step is only one part the production process. The development of a novel technique which cannot be linked properly with other unit operations in the production process may lose its best performance when integrated in the complete sequence of operations for productions. Integration of a continuous-flow reactor in a setup (*e.g.* with separation equipment) which could fit in a fume hood would be perfect for small-scale production (*i.e.* mini-plant). Therefore, this fume hood concept would be an ideal starting point for scaling-up fine chemical production processes.

This fume hood concept is an approach which preferably minimizes the scaling-up factor and the issues concerning scalability. The fume hood concept consists of individual unit operations flexibly linked in time or in place related to the requirements of the production process. The most common approach is a continuously operated setup where various unit operations are spatially linked. After all, the distance of a selected segment in the continuous operation measured from feed or from end product in the overall processing determines the progress.

An alternative for a multi-purpose continuously operated process is pipeless operation in a manufacturing plant.[53] The reactors are mobile and the additional values are given in time after each other. The theory behind the development of pipeless operations is not further elaborated in this fume hood concept.

To be more specific for the fume hood approach for a spatially linked continuous operation, reaction times are preferably relatively short till medium long (< 3 h). Time constants for reaction and downstream processing should be tuned as well as possible. Storage vessels will occasionally be necessary. Moreover, each operational step would ideally be energy efficient with high atom efficiency. For example, extractions consume large volumes of solvents (if not recycled) and isolation of the product by distillation may consume considerable amounts of energy.

Obviously, most of these requirements hold for the current batchwise operation on industrial scale. However, a switch to continuous operations improves the control over process parameters (*e.g.* temperature) at any stage.

In the next section the basic setup with several modifications and possible extensions will be discussed stepwise.
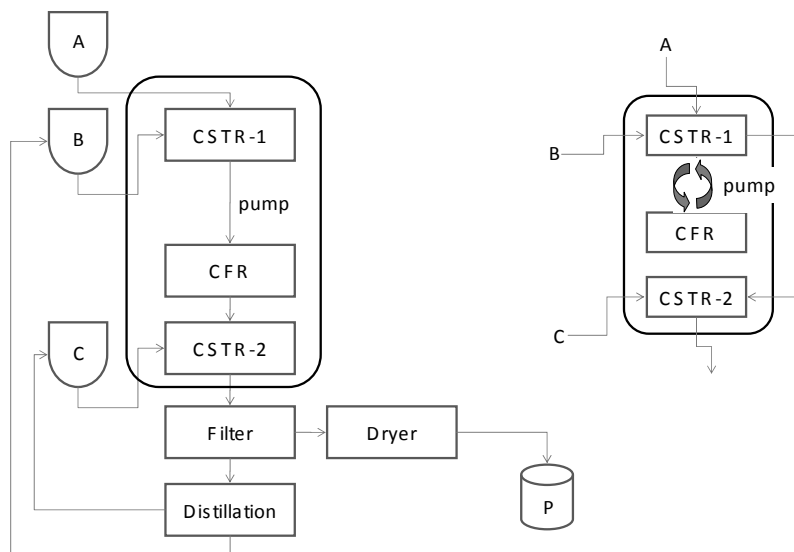
**Figure 5.7**    *Flow diagrams of a basic setup of a fume hood concept; (left) as a continuous process, (right) as a batch-loop process.*

<u>**Basic setup**</u>

Figure 5.7 (left) shows a basic process flow diagram of the fume hood where the microwave-heated continuous-flow reactor (CFR) is the central unit. The CFR is continuously operated with relatively short reaction times (< 30 min) or when optimal production rates for slower reactions can be obtained with relatively short reaction times. The CFR is fed via CSTR-1, a pre-mixer for reactant A (solid/liquid) and B (liquid). Gases can be introduced downstream with respect to the pump in combination with a static mixer.

> *<u>Modification (1):</u> Processes demanding longer reaction times can make use of a recycle loop (Figure 5.7 (right)). The outlet of CFR is recycled to CSTR-1. The system is now in a batch-loop operation mode. After completion a connection of CSTR-1 to CSTR-2 is made. Each CSTR can be replaced with in-line static mixers.*

After reaction in the CFR another stream (C) can be introduced. Beyond this stage the product/intermediate should be in a physical state to enable separation from the remaining reaction mixture, *e.g.* by centrifugation, filtration or extraction.

CSTR-2 in combination with an anti-solvent stream of C (and if necessary cooling of the vessel wall) simplifies this setup for precipitation or as a possible continuous crystallizer.

*Modification (2): The replacement of CSTR-2 by two parallel columns (containing functionalized resin) allows this setup to separate the product from the reaction mixture in one column while simultaneously regenerating the other column. A similar approach can be adapted for ultra-filtration or other (selective) membrane filtrations.*

The product can be isolated or continuously fed as a stream to *e.g.* a dryer. The other streams might be considered for recycling.

*Extension: More flexibility and production volume are introduced when parallel units are interconnected which upgrades the possibilities of the basic concept.*

Two reactions demonstrate the feasibility of such a fume hood concept by fitting the processes as an exercise. One process involves the *O*-acetylation of salicylic acid which is the final step in the synthesis of aspirin, see Scheme 5.1; the other represents the Laurydone process, see also chapter 2.7.
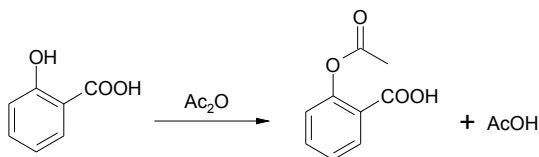


**Scheme 5.1**     *Synthesis of Aspirin; O-acetylation of salicylic acid.*

### *O*-acetylation of salicylic acid

The process flow diagram in Figure 5.7 (left) illustrates a basis for the continuous production of aspirin (Scheme 5.2). The aspirin production is an example for a large-scale synthesis.[54,55] Salicylic acid is continuously charged as solid A. Stream B represents an amount of acetic anhydride (dissolved in acetic acid) per time-unit, equimolar (or more equivalents) with respect to stream A. The reaction can be catalyzed by acids or bases; the first type of catalysis is preferred in view of atom efficiency (otherwise twofold deprotonation is required). The catalyst can be homogeneous or heterogeneous *i.e.* an acid-functionalized macroporous resin incorporated in the CFR. Self-catalysis by salicylic acid is also a possibility in this case. After reaction, at a certain temperature and residence time (< 30 min), the mixture can be diluted with an anti-solvent (water) or directly cooled. Aspirin crystallizes and the slurry can be concentrated or filtered and additionally washed in a centrifuge (or belt-filter). Subsequently, the product is dried (*e.g.* by microwave heating) to remove the remaining solvents. Finally, water can be removed from the recycle stream via pervaporation.[56]

An actual running process (35 kt/a) for the acetylation of salicylic acid is shown in Figure 5.8.[57]
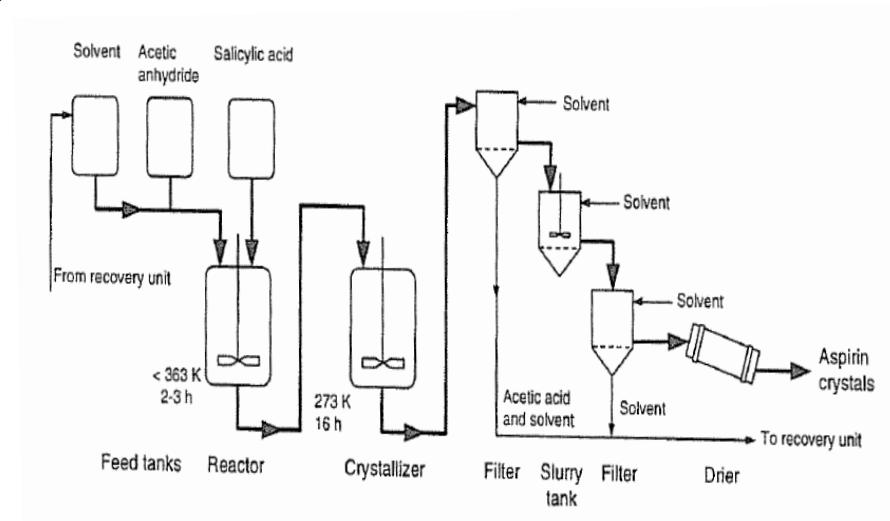


**Figure 5.8**   *Simplified scheme of aspirin production (batch process).*[57]

**Laurydone process**
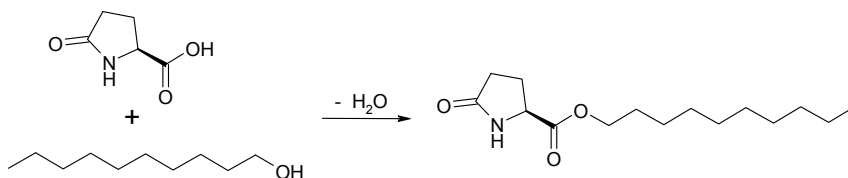


**Scheme 5.2**   *Reaction of (S)-pyroglutamic acid with n-decanol.*

For the Laurydone process the introduction of a loop (Figure 5.7 (right)) is necessary due to a long reaction time (3 h). A direct start with an equimolar mixture (Scheme 5.2) of (S)-pyroglutamic acid and *n*-decanol leads to plugging at ambient temperatures. Preferably, preheating of *n*-decanol with a gradual addition of (S)-pyroglutamic acid overcomes this problem. Thereafter, an overflow to CSTR-2 is opened to collect the enriched stream with product. By applying vacuum the remaining water and *n*-decanol can be separated from the reaction mixture. The product crystallizes by cooling or by feeding anti-solvent (water). Cooling can be done in the filter unit to prevent clogging in CSTR-2 which arises due to a high weight ratio of product. The remaining (S)-pyroglutamic acid is removed from the desired ester product by washing with water.

## 5.7 Concluding remarks

From a technical point of view scaling-up heterogeneous reactions by microwave irradiation is feasible. It is not only possible to rapidly heat the reaction mixture, but the experimentally observed batch data of the time - conversion history can also be used for process design including a preserved microwave effect (see Chapter 6).

The transfer of microwave energy into heat, directly or indirectly via the Weflon blades, allows the use of any kind of reaction mixture in terms of polarity or loss tangent. The combination of stirring and heating gives rise to an uniform and efficient energy transfer. The residence time distribution of the CFR results in a performance (with a single pass) equivalent to that of a series of three CSTR's (section 5.5). If plug-flow is desired then a reactor with a smaller diameter without stirrer has to be developed. Optional, in further modification of the tubular reactor, is the implementation of a static mixer‡ (*e.g.* made of microwave-absorbing material such as Weflon).

Plugging as a result of precipitation of reactants or products is a point of attention in process design. Redesigning the equipment, involving Teflon-coating and thermostatic tracing, may overcome this risky obstacle. Even operations at a slightly larger scale than the currently used CFR allow an acceptable ratio between the inner diameter (> 5 mm) of the equipment and the particle size of the solid substrates.

The CFR in a fume hood concept is ideal for a mini-plant setup where energy consumption is not determining the main costs. Direct temperature control and the opportunity to quench the reaction easily are highly advantageous.

Recalculating the operational costs is necessary to decide whether microwave heating is still beneficial if larger production scales are planned. In general the chances to incorporate microwave heating as a competitive technique seem to decrease for larger scales. Although in some cases, safety can be considered as a decisive parameter in the overall decision process, see the DuPont case (section 5.4).[47]

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‡ *Typical examples of static mixers in e.g. polymer processing are made by Sulzer (Chemtech) Ltd, Winterthur, Switzerland.*

## 5.8 Experimental data

*The continuous-flow reactor has been supplied by Milestone srl, Italy. The tubular reactor can either be equipped with a Teflon or a Weflon stirrer. The original setup includes a membrane pump of Alldos GmbH (now known under the name Grundfos); type 281-9,6-1004; 100 bar; 50 Hz. Physical constants are obtained from Handbook of Chemistry and Physics; 89th Edition; **2008-2009** (online edition, Lide, D. R.).*

**Table 5.4**  *Relationship between energy efficiency and operational conditions of CFR for p-xylene (a) without stirring and (b) with stirring.[†] Only performed with Weflon stirrer.*

| entry | stirrer speed (rpm) | | flow rate ($10^{-3}$ kg.s$^{-1}$) | power input (W) | $\Delta T$ (K) | | efficiency (%) | |
|---|---|---|---|---|---|---|---|---|
| | (a) | (b) | | | (a) | (b) | (a) | (b) |
| 1 | 0 | 195 | 0.75 | 200 | 53 | 81 | 34 | 52 |
| 2 | 0 | 195 | 0.75 | 400/600/800 | ‡ | ‡ | - | - |
| 3 | 0 | 195 | 1.61 | 200 | 34 | 53 | 47 | 73 |
| 4 | 0 | 195 | 1.61 | 400 | 57 | 101 | 39 | 69 |
| 5 | 0 | 195 | 1.61 | 600/800 | ‡ | ‡ | - | - |
| 6 | 0 | 195 | 2.26 | 200 | 34 | 37 | 66 | 71 |
| 7 | 0 | 195 | 2.26 | 400 | 55 | 70 | 53 | 67 |
| 8 | 0 | 195 | 2.26 | 600 | 68 | 101 | 44 | 65 |
| 9 | 0 | 195 | 2.26 | 800 | ‡ | ‡ | - | - |
| 10 | 0 | 195 | 2.82 | 200 | 23 | 25 | 55 | 60 |
| 11 | 0 | 195 | 2.82 | 400 | 48 | 62 | 58 | 75 |
| 12 | 0 | 195 | 2.82 | 600 | 62 | 92 | 50 | 74 |
| 13 | 0 | 195 | 2.82 | 800 | 77 | 105 | 46 | 63 |

† $c_P$ (p-xylene) = 1709 J.kg$^{-1}$.K$^{-1}$

‡ Steady state not reached (below 130 °C, which was set as operational maximum)

**Table 5.5**    *Relationship between energy efficiency and operational conditions of CFR for demi-water with (a) Weflon and (b) Teflon stirrer.[†]*

| entry | stirrer speed (rpm) | | flow rate ($10^{-3}$ kg.s$^{-1}$) | power input (W) | $\Delta T$ (K) | | efficiency (%) | |
|---|---|---|---|---|---|---|---|---|
| | (a) | (b) | | | (a) | (b) | (a) | (b) |
| 1 | 195 | 195 | 1.04 | 200 | 39 | 28 | 85 | 61 |
| 2 | 195 | 195 | 1.04 | 400 | 80 | 62 | 87 | 67 |
| 3 | 195 | 195 | 1.04 | 600/800 | ‡ | ‡ | - | - |
| 4 | 195 | 195 | 1.92 | 200 | 18 | 23 | 72 | 92 |
| 5 | 195 | 195 | 1.92 | 400 | 42 | 42 | 84 | 84 |
| 6 | 195 | 195 | 1.92 | 600 | 66 | 68 | 88 | 91 |
| 7 | 195 | 195 | 1.92 | 800 | 81 | 84 | 81 | 84 |
| 8 | 195 | 195 | 2.78 | 200 | 12 | 14 | 70 | 81 |
| 9 | 195 | 195 | 2.78 | 400 | 29 | 30 | 84 | 87 |
| 10 | 195 | 195 | 2.78 | 600 | 44 | 46 | 85 | 89 |
| 11 | 195 | 195 | 2.78 | 800 | 56 | 63 | 81 | 91 |
| 12 | 195 | 195 | 3.33 | 200 | 10 | 12 | 70 | 84 |
| 13 | 195 | 195 | 3.33 | 400 | 24 | 26 | 84 | 91 |
| 14 | 195 | 195 | 3.33 | 600 | 38 | 41 | 88 | 95 |
| 15 | 195 | 195 | 3.33 | 800 | 51 | 53 | 89 | 92 |

† $c_P$ (water) = 4180 J.kg$^{-1}$.K$^{-1}$

‡ *Steady state not reached (below 110 °C, which was set as operational maximum)*

**Table 5.6**    *Relationship between energy efficiency and operational conditions of CFR for ethylene glycol (only with Weflon stirrer).[†]*

| entry | stirrer speed (rpm) | flow rate ($10^{-3}$ kg.s$^{-1}$) | power input (W) | $\Delta T$ (K) | efficiency* (%) |
|---|---|---|---|---|---|
| 1 | 195 | 1.08 | 200 | 49 | 63 |
| 2 | 195 | 1.08 | 400 | 100 | 65 |
| 3 | 195 | 1.08 | 600/800 | ‡ | - |
| 4 | 195 | 2.44 | 200 | 31 | 91 |
| 5 | 195 | 2.44 | 400 | 63 | 92 |
| 6 | 195 | 2.44 | 600 | 92 | 90 |
| 7 | 195 | 2.44 | 800 | 115 | 84 |
| 8 | 195 | 2.73 | 200 | 30 | 110 |
| 9 | 195 | 2.73 | 400 | 58 | 106 |
| 10 | 195 | 2.73 | 600 | 85 | 104 |
| 11 | 195 | 2.73 | 800 | 108 | 99 |
| 12 | 195 | 3.28 | 200 | 22 | 97 |
| 13 | 195 | 3.28 | 400 | 47 | 103 |
| 14 | 195 | 3.28 | 600 | 72 | 105 |
| 15 | 195 | 3.28 | 800 | 92 | 101 |

† $c_P$ (ethylene glycol) = 2394 J.kg$^{-1}$.K$^{-1}$;

‡ *Steady state not reached (below 140 °C, which was set as operational maximum)*

* *The error margin of these measured values is in the range of 5-10 %*

**Table 5.7**    *Relationship of flow rate and stirrer speed with the number of equally sized tanks in series.*

| entry | flow rate (mL.min⁻¹) | stirrer speed (rpm) | reactors in series (number) | remark |
|-------|----------------------|---------------------|-----------------------------|--------|
| 1  | 191 | 0   | 3.0 | - |
| 2  | 191 | 140 | 4.9 | - |
| 3  | 191 | 215 | 5.3 | - |
| 4  | 191 | 285 | 2.4 | *splitted peak* |
| 5  | 191 | 327 | 1.8 | *shoulder* |
| 6  | 191 | 380 | 2.3 | - |
| 7  | 214 | 0   | 3.7 | - |
| 8  | 214 | 140 | 3.6 | *splitted peak* |
| 9  | 214 | 215 | 2.5 | *splitted peak* |
| 10 | 214 | 327 | 4.2 | *shoulder* |
| 11 | 232 | 0   | 3.5 | *splitted peak* |
| 12 | 232 | 140 | 3.9 | *shoulder* |
| 13 | 232 | 215 | 2.9 | *shoulder* |



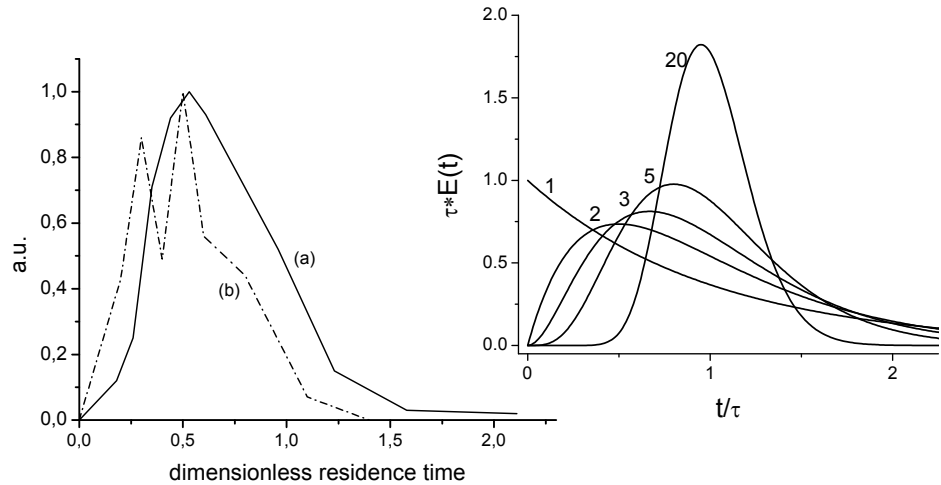**Figure 5.9**    *(left) Exit-age function E(t) for the FlowSynth with Weflon impeller blades (see Figure 5.6): (a) typical plot with small disturbance [Table 5.7 entry 2]. (b) large disturbance in tubular reactor leading to enhanced axial mixing [Table 5.7 entry 8]; normalized at the intensity (a.u. arbitrary units). (right) Theoretical residence time distribution with an increasing number of tanks (n = 1,2,3,5 and 20).*

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# Chapter 6

**6**

# Performance of a microwave-heated flow reactor

## Abstract

Heterogeneous reactions on the one hand represent the majority of fine chemical processes and on the other may give rise to potentially significant microwave effects. However, exactly this reaction type requires the most effort and adaptation under continuous operation.

Nevertheless, a series of four reactions has been studied in an adapted, commercially available continuous-flow reactor. The (homogeneous) aspirin synthesis and a (heterogeneous) biocatalyzed, enantioselective transesterification successfully demonstrated a close correlation in reaction rate between batch-performed and continuous processing. The Laurydone process (47 wt % substrate) ran in a more diluted (10 wt % substrate) condition with a similar reaction rate. However, the removal of the formed water remained a limiting factor in the final stage of the conversion.

Although the (heterogeneous) racemization of *N*-acetylindoline-2-carboxylic acid retained its microwave effect under continuous operation, plugging has to be dealt with.

Technological solutions are demanded to improve the current setup, while an increase of the dimensions thereof may also contribute to an even better feasibility of the fume hood concept.

In general, the results described in this chapter demonstrate that microwave-assisted, heterogeneous batch reactions are easily translated to microwave-assisted flow processing.

6

## 6.1 Introduction

In literature the application of the FlowSynth developed by Milestone to accommodate organic processes has been reported. Typical example are the esterification of carboxylic acids with dimethyl carbonate[1-3] or the esterification of acetic acid with butanol.[4] More examples in organic chemistry can be found in a review of Glasnov and Kappe.[5] In particular the Weflon blades combined with the helical coil enable efficient heat transfer and mass transport in the tubular reactor that is positioned in the microwave oven, see Figure 5.6 in the previous chapter. Also handling of heterogeneous reactions is feasible with this setup.

From the results described in the chapters 2, 3 and 4 it was concluded that beneficial microwave effects were only observed when heterogeneity plays a crucial role in the rate-determining step. All of the heterogeneous reactions reported in the chapters 2, 3 and 4 were originally performed batchwise on a relatively small scale (< 20 mL) in the Milestone MicroSynth. Only a few examples were selected from our study to assess the scalability of these heterogeneous reactions in the FlowSynth.

In chapter 5 the characteristics of the continuous-flow reactor FlowSynth have been described. The initial experimental results discussed in chapter 5 looked very promising. However, bringing the continuous-flow reactor to a next level closer to commercial scale *e.g.* larger temperature differences, higher solid content and lower solubilities, have put forward new challenges (*e.g.* solid and slurry handling). Consequently, "the proof of the pudding is in the eating" and each studied reaction will be separately discussed in the next sections.

## 6.2 Biocatalyzed esterification

In chapter 2 esterifications have been discussed with three types of biocatalysts. Novozym 435 (*Candida Antarctica* lipase B on a resin) was preferred as a catalyst over other types of enzymes (chapter 2.3). The choice of Novozym 435 was based on stability, activity and accessibility. It was demonstrated that the enantioselective esterification of commercially available (*R*,*S*)-1-phenylethanol with vinyl acetate in toluene is relatively fast (Scheme 6.1 and chapter 2.3). Similar to the batch experiments an excess of vinyl acetate was used for reactions in the FlowSynth to enforce a high conversion within a reasonable time interval (2-3 hours). Changes in conversion or temperature do not have a profound effect on the heterogeneity during the experiments.
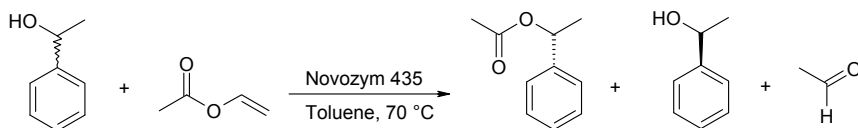
**Scheme 6.1** *Esterification of (R,S)-1-phenylethanol with vinyl acetate in an enantio-selective reaction using Novozym 435.*

The continuous-flow experiment (0.4 mol) has been scaled up by a factor of 100 with respect to the batch mode reaction (4 mmol). The reaction mixture without biocatalyst was premixed in a 1 L round-bottomed flask and magnetically stirred. After a short period this homogeneous mixture was pumped through the loop. The reaction temperature in the top of the tubular reactor ($T^1$) was set at 70 °C. The microwave power was automatically adjusted to maintain the temperature at $T^1$ of this set point, see Figure 6.1.
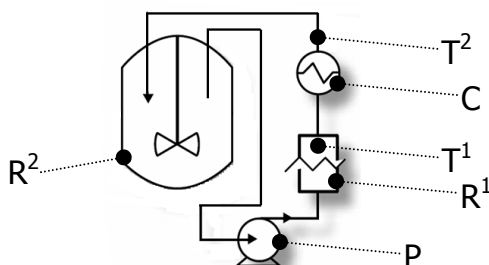


**Figure 6.1** *Batch-loop reactor setup for the esterification of (R,S)-1-phenylethanol with vinyl acetate: $R^1$ = microwave-heated tubular reactor; $R^2$ = round-bottomed flask with magnetic stirrer; P = (membrane-)pump; C = cooler with Archimedes´ screw; $T^1$ = temperature sensor inside the upper part of the tubular reactor and $T^2$ = temperature sensor just downstream the cooler.*

The esterification was performed twice (experiments A and B) in the FlowSynth. In experiment A the reaction mixture should have been distributed evenly over the batch-loop setup. In experiment B the catalyst is retained on purpose in the microwave-heated tubular reactor ($R^1$).

Experiment A
The flow rate has been measured before and after the addition of Novozym 435. In both cases the flow rate was 175 mL.min$^{-1}$. Once the reaction setup reached a steady state (in which the temperature was constant in time) Novozym 435 was charged to flask $R^2$. During the reaction aliquots were taken just after point $T^2$, but before vessel $R^2$ (see Figure 6.1). The time – conversion history is plotted in Figure

116

6.2. It is noteworthy to mention that the amount of Novozym 435 appeared to be higher inside the reactor than in vessel $R^2$ or outside $R^1$. The liquid velocity in the tubing ($v_{tub}$ = 0.15 m.s$^{-1}$) was considerably higher compared to that in the tubular reactor ($v_{react}$ = 0.012 m.s$^{-1}$), which might explain settling of Novozym 435 in the column $R^1$. The narrow exit after $T^2$ can also lead to a hold-up or plugging of the spherical particles of Novozym 435. The temperature in vessel $R^2$ has been monitored manually and never exceeded 30 °C.



**Figure 6.2**    *Esterification of (R,S)-1-phenylethanol with vinyl acetate in toluene at 70 °C catalyzed by Novozym 435 in (a) an oil-bath-heated batch reactor (4 mmol scale); (R)-1-phenylethyl acetate ($-\blacktriangle-$) and (Exp. A) in a microwave-heated batch-loop reactor (0.4 mol scale) at $\phi_v$= 0.175 L.min$^{-1}$; (R)-1-phenylethyl acetate ($-\blacksquare-$).*

The total reaction volume was 0.940 L and the volume of the tubular reactor was 0.180 L. With a flow rate of 0.175 L.min$^{-1}$ and a total reaction time of 173 min, the number of cycles was calculated to be 168 with an average residence time of a little more than one minute per cycle in column $R^1$. Subsequently, for this batch-loop reactor experiment only 19 %[‡] of the reaction mixture was exposed to the temperature of 70 °C. In the batch experiment, however, 100 % of the reaction mixture was subjected to a temperature of 70 °C. The uneven distribution of Novozym 435 over the complete reaction mixture hampers a quantitative comparison of the reaction rates for thermal and microwave heating.

Note that comparison of the batch experiments with respect to both heating methods as described in chapter 2 demonstrated the absence of a rate enhancement effect by microwave heating.

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[‡] $V_R^1/V_{tot}$ = 0.19 (fractional residence time)

Experiment B

The procedure applied in Exp. A was repeated for the esterification in the continuous-flow reactor in a batch-loop mode. Now, Novozym 435 was charged directly into the tubular reactor and the reactor was put together to operate under flow conditions with complete retention of the Novozym 435 inside the microwave cavity. The reactor content was not stirred.

During the reaction aliquots were taken after point $T^2$, but before vessel $R^2$. The results are plotted in Figure 6.3.
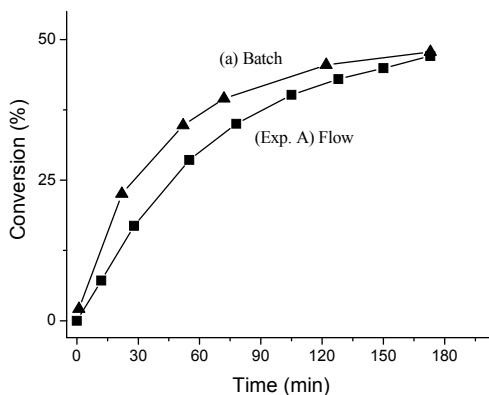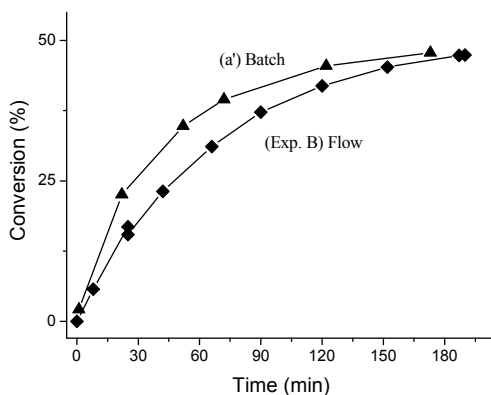


**Figure 6.3**    *Esterification of (R,S)-1-phenylethanol (4 mmol) with vinyl acetate in toluene at 70 °C catalyzed by Novozym 435 in (a) an oil bath-heated batch reactor; (R)-1-phenylethyl acetate (—▲—) and (Exp. B) in a microwave-heated batch-loop reactor (0.4 mol) with catalyst charged in the tubular reactor at $\phi_v$= 0.12 L.min$^{-1}$; (R)-1-phenylethyl acetate (—◆—).*

The time-conversion history in Figure 6.3 is comparable with that of Figure 6.2. This observation confirms that the majority of the solid particles in the experimental setup for experiment A could have been retained in the tubular reactor. In contrast to the batch experiment the concentration of the biocatalyst has been locally increased with a factor of 5.2. The total mean residence time per pass has decreased with the same factor. These two changes cancel out each other.

The remaining difference in reaction rate is partially related to either a small temperature gradient in the microwave-heated tubular reactor or to some mass transfer limitations inside the reactor (without stirring). Without stirring (and with a laminar flow) the regime of (intraparticle) mass transport limitation can change, as a result of a change of the global reaction order (see Figure 6.4 (left)).[6] Figure 6.4 (right) illustrates the effect of transport limitation to or from the particles on the time-conversion.[7]
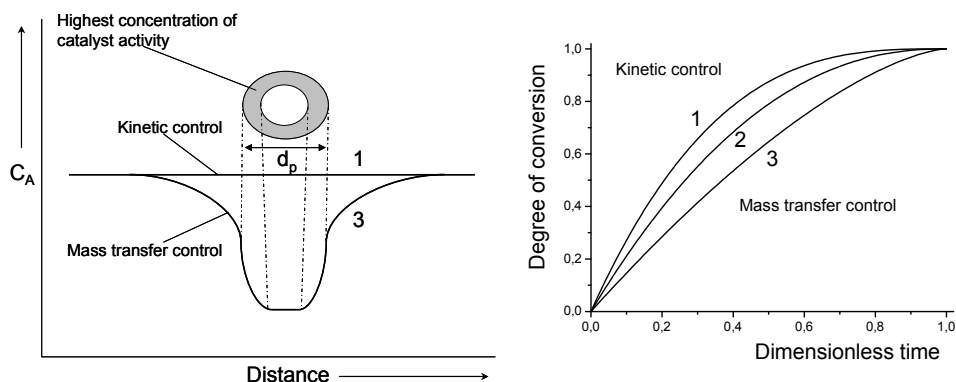
**Figure 6.4** *(left) Concentration profile ($C_A$) around and inside of a catalyst particle (with shell catalyst such as Novozym 435) with strong mass transfer limitation (3) and with intrinsic kinetics (1). (right) Dimensionless time - conversion profiles of a first-order reaction based on the concentration of a solid (partially dissolved) and the rate-determining regime (1-3).* [7]

In general, Michaelis-Menten kinetics is applicable to this system, meaning that for the applied substrate concentration pseudo first-order kinetics can be used to describe the conversion with time. In our case the substrate concentration appeared not to limit the activity of the enzyme.[8]

This example of a biocatalytic esterification exemplifies a direct correlation between batch and continuous operation. Approximately the same final conversions are achieved for comparable reaction times.

## 6.3 Racemization of (*S*)-*N*-acetylindoline-2-carboxylic acid

In contrast to the biocatalytic conversion as described in chapter 6.2, heterogeneity of a reaction is now governed by the substrate and its solubility during the racemization of *(S)-N*-acetylindoline-2-carboxylic acid, see Scheme 6.2.
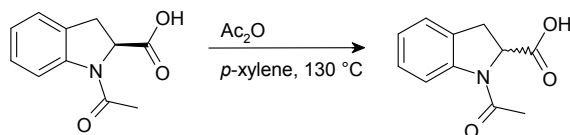


**Scheme 6.2** *Racemization of (S)-N-acetylindoline-2-carboxylic acid.*

Changes in reaction conditions such as temperature or co-solvent influence the performance of the batch-loop reactor (Figure 6.5), including factors such as plugging.
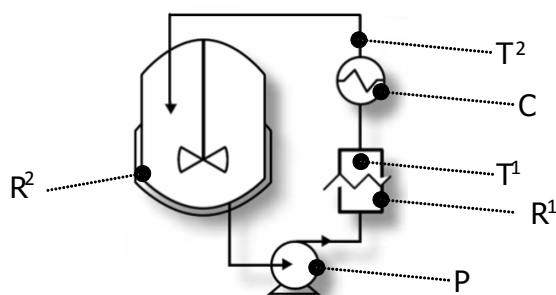
**Figure 6.5**    *Batch-loop reactor setup for the racemization of (S)-N-acetylindoline-2-carboxylic acid: $R^1$ = microwave-heated tubular reactor; $R^2$ = double-walled reactor vessel with mechanical pitched-blade impeller; P = (membrane-)pump; C = cooler with Archimedes´ screw; $T^1$ = temperature sensor inside the upper part of the tubular reactor and $T^2$ = temperature sensor just downstream the cooler.*

Two racemization experiments under different conditions were performed with (*S*)-*N*-acetylindoline-2-carboxylic acid as substrate, see Table 6.1. For both reaction conditions a microwave effect was expected based on already described experimental results, see chapter 3.

**Table 6.1**    *Racemization of (S)-N-acetylindoline-2-carboxylic acid performed at different reaction conditions in the continuous-flow reactor in a batch-loop mode.*

| entry | parameters | experiment A | experiment B |
|---|---|---|---|
| 1 | *(S)-N-acetylindoline-2-carboxylic acid* | *178 g (S)* | *126 g (S)* |
| | | *0.87 mol* | *0.62 mol* |
| 2 | *p-xylene* | *679 g* | *650 g* |
| 3 | *acetic acid* | * | *72 g* |
| 4 | *acetic anhydride* | *22.3 g* | *14.8 g* |
| | | *0.22 mol* | *0.14 mol* |
| 5 | *wt % substrate* | *21* | *15* |
| 6 | *wt % co-solvent (acetic acid)* | * | *10* |
| 7 | *flow rate* | *216 mL.min$^{-1}$* | *222 mL.min$^{-1}$* |
| 8 | *total reaction time* | *263 min* | *182 min* |
| 9 | *interruption by:* | *plugging* | *plugging* |

* *small amount of water present, which produces acetic acid from acetic anhydride (< 2 wt%).*

Although each run was prematurely aborted due to plugging, sampling allowed comparison with the batch experiments. The main difference between experiment A and B was the amount of co-solvent. In experiment A the racemization was

performed without co-solvent. In experiment B acetic acid was added to decrease the heterogeneity, and therefore to reduce the microwave effect and the risks of plugging.

Experiment A

In this experiment the racemization was performed without co-solvent. After addition of the catalyst (acetic anhydride) a fast decrease of the enantiomeric excess was observed in the small-scale batch experiments (Figures 6.6(a) and (b)) in the first period (< 60 min). Subsequently, the racemization during the microwave-heated experiment continued, but for conventional heating inhibition was temporarily observed. After 120 min the reaction rate of racemization increased as the solubility of the substrate rose. For the small-scale batch reaction conventional and microwave heating gave rise to different reaction rates. The flow experiment behaved similarly to the microwave-heated batch experiment as illustrated by the absence of an inhibition period after the addition of the catalyst. Reaction rates based on enantiomeric excess changes from 90 to 70 % ee are shown in Table 6.2 for both the batch experiments and the continuous-flow experiment A.
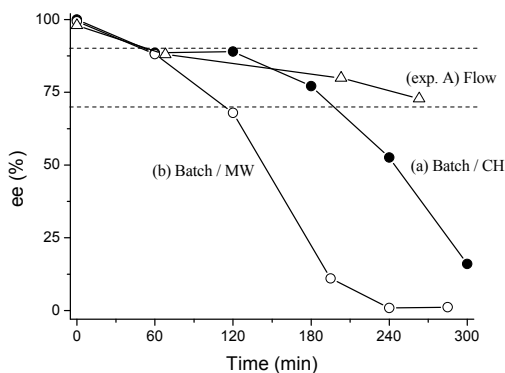


**Figure 6.6**    *Racemization of N-acetylindoline-2-carboxylic acid at 130 °C in (exp. A) continuous-flow experiment in a batch-loop mode, (a) conventionally heated batch experiment and (b) microwave-heated batch experiment. Experiments were performed under comparable conditions, see Table 6.1.*

Ideally, experiment A should have gone to completion to demonstrate that complete racemization can take place in the continuous-flow reactor. However, plugging urged preliminary interruption of experiment A. Experience from earlier racemization experiments as described in chapter 3 taught us that inhibition is only observed during the initial period, after which the reaction goes to completion. This observation - combined with the relative reaction rates - shows that the

conversions in the continuous-flow reactor closely resemble those of the microwave-heated small-scale batch experiment. In this case, in contrast to the biocatalytic reaction described in section 6.2, racemization can in principle partially continue outside the tubular reactor, before a temperature is reached at which the rate of racemization is negligible. However, continuation of the racemization outside the microwave-heated tubular reactor $R^1$ is insufficient to distinguish it from the measurement error.

**Table 6.2** *Reaction rates (interval between 90 and 70 % ee) of the racemization of (S)-N-acetylindoline-2-carboxylic acid under conventional and under microwave heating conditions.*

| entry | conditions | overall reaction rate [$\Delta$ee.min$^{-1}$] | fractional residence time* | corrected reaction rate [$\Delta$ee.min$^{-1}$] |
|---|---|---|---|---|
| 1 | batch (a); CH | -0.20 | 1 | -0.20 |
| 2 | batch (b); MW | -0.34 | 1 | -0.34 |
| 3 | experiment A | -0.08 | 0.21 | -0.36 |

\* *fractional residence time in the reactor compared to the total reaction time [based on the ratio of the volume of the microwave-heated tubular reactor ($R^1$, 180 mL) per total reaction volume (850 mL); overall rate = $V_{R^1}/V_{tot} \cdot$ rate (MW, $R^1$) ]*

Experiment B

In experiment B acetic acid was added to reduce the heterogeneity of the system. After addition of the catalyst (acetic anhydride) some technical problems occurred. The reaction mixture was temporarily collected in one vessel and at a temperature below 20 °C. The system was restarted and two large aliquots were taken to perform two experiments batchwise by oil-bath heating at 60 °C and 122 °C, see Figure 6.7. As a result of these large aliquots, the total reaction volume in the microwave-heated batch-loop system was less than in experiment A. As a consequence the fractional residence time (= real reaction time) in tubular reactor $R^1$ (Figure 6.5) was higher than in experiment A, see Table 6.3 [entry 4]. Experiment B was executed at 127 °C in the continuous-flow reactor. The temperature in vessel $R^2$ (Figure 6.5) was below 60 °C (manually measured). The low reaction rate at 60 °C (Figure 6.7) allows neglecting racemization in vessel $R^2$. The inhibition period as observed for the conventionally heated racemization in experiment A was not observed (see Figure 6.6), due to the delay of sampling. Reaction rates based on an enantiomeric excess change from 86 to 34 % ee (area between dotted lines in Figure 6.6) were compared between three batch experiments (c, d, e) and the continuous-flow experiment B (Table 6.3).

**Table 6.3** *Reaction rates (interval of 86 and 34 % ee) of the racemization of N-acetylindoline-2-carboxylic acid under different reaction conditions.*

| entry | conditions | overall reaction rate [$\Delta$ee.min$^{-1}$] | fractional residence time* | corrected reaction rate [$\Delta$ee.min$^{-1}$] |
|---|---|---|---|---|
| 1 | batch (c); CH (60 °C) | *-0.015* | *1* | *-0.015* |
| 2 | batch (d); CH (122 °C) | *-1.26* | *1* | *-1.26* |
| 3 | batch (e); MW (129 °C)** | *-2.05* | *1* | *-2.05* |
| 4 | experiment B (127 °C) | *-0.55* | *0.23* | *-2.43* |

\* *fractional residence time in the reactor compared to the total reaction time [based on the ratio of the volume of the microwave-heated tubular reactor ($R^1$, 180 mL) per total reaction volume\*\*\* (785 mL); overall rate $= V_{R^1}/V_{tot} \cdot$ rate (MW, $R^1$).*

\*\* *reaction rate observed under microwave heating and comparable conditions.*

\*\*\* $V_{tot} = V_{premixed} - V_{sampling}$ *; 785 mL = 850 mL – 65 mL.*
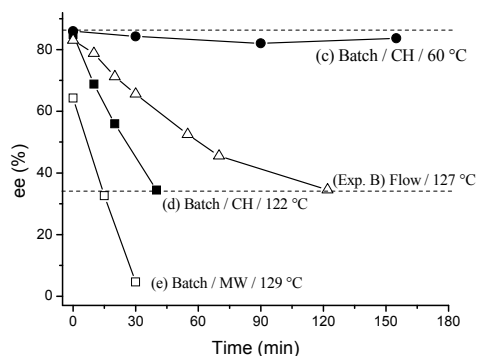


**Figure 6.7** *Racemization of (S)-N-acetylindoline-2-carboxylic acid in a continuous-flow experiment in batch-loop mode (Exp. B) compared to (c) conventionally heated run at 60 °C, (d) conventionally heated run at 122 °C batch experiment, and (e) microwave-heated run at 129 °C, all under comparable conditions.*

Experiment B allows us to make a fair comparison between microwave and conventional heating of the racemization efficiency during a longer period (with respect to Exp. A) on the basis of changes of the enantiomeric excess. Again the estimated conversion of the microwave-heated experiment proved to be in line with expectations.

The racemization was effective during a longer period and in a larger volume outside the microwave-heated tubular reactor $R^1$, due to the deliberate absence of cooling power in cooler C (Figure 6.5) as compared to experiment A.

In summary, based on the experiments discussed in this section it can be concluded that the microwave effect described in chapter 3 has been demonstrated in the

continuous-flow reactor with respect to larger scale applications. Thus for the racemization microwave heating is preferable to conventional heating for either batch or continuous operation.

## 6.4 Laurydone process

The only example in the field of microwave-assisted fine chemical applications is the Laurydone process.[9] This example illustrates the possibility to apply mic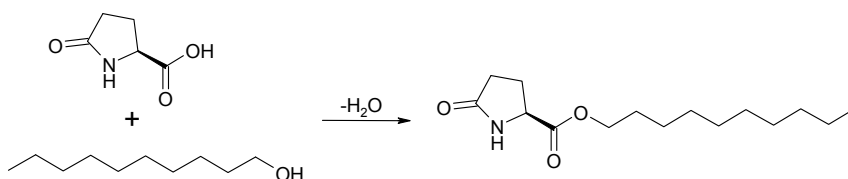rowave heating on a large scale. Despite the successful large-scale operations with microwave heating, the originators failed to show the superiority of microwave heating technology over conventional heating. In chapter 2.6 this conclusion was elaborated in more detail.



**Scheme 6.3**    *Esterification of (S)-pyroglutamic acid with n-decanol.*

All our batch reactions of the Laurydone synthesis have been performed with a high concentration of substrate ((*S*)-pyroglutamic acid) in *n*-decanol. Such a solid weight percentage (47 wt%) appeared to be impractical to handle in the continuous-flow reactor. Reduction of the acid weight percentage to 10 wt% guaranteed a smooth flow for the initially heterogeneous reaction mixture, see Scheme 6.3. Again two different conditions have been applied for this type of esterification (Table 6.4). It is important to point out that the membrane pump in experiment A was replaced by a better functioning gear pump in experiment B. Compared to a membrane pump a gear pump is more suitable for handling more viscous mixtures, like *n*-decanol. The flow schemes of the setup for experiments A and B are schematically depicted in Figures 6.1 and 6.5, respectively.

**Table 6.4**    *Esterification of (S)-pyroglutamic acid with n-decanol under different reaction conditions (Exp. A and Exp. B) in the continuous-flow reactor operated in a batch-loop mode.*

| entry | parameters | experiment A | experiment B |
|-------|-----------|--------------|--------------|
| 1 | *(S)-pyroglutamic acid* | *69.1 g* | *69.0 g* |
|   |   | *0.54 mol* | *0.53 mol* |
| 2 | *n-decanol* | *622 g* | *622 g* |
|   |   | *3.93 mol* | *3.93 mol* |
| 3 | *wt % substrate* | *10* | *10* |
| 4 | *flow rate* | *115 mL.min$^{-1}$* | *343 mL.min$^{-1}$* |
| 5 | *pump* | *membrane* | *gear* |
| 6 | *total reaction time* | *140 min* | *178 min* |
| 7 | *mixing speed R$^2$ /suction line from R$^2$* | *medium/bottom* | *low/top* |
| 8 | *interruption:* | *plugging* | *manual* |

Experiment A

After charging vessel R$^2$ with reactants and stirring with a mechanical impeller, the resulting solid/liquid mixture was pumped through the tubular reactor (without heating). This procedure enabled to run the flow system for many hours without any complications. Subsequently, heating was applied to the tubular reactor R$^1$ (Figure 6.5, 150 °C). Cooling agent of 8 °C was supplied to the jacket of cooler C and cooling of vessel R$^2$ was started by pumping a coolant of 12 °C through the jacket. Shortly after starting up the heating and cooling, plugging occurred in the cooler C. This prevented any flow. Also stirring of the coil in the tubular continuous-flow reactor was not possible. A deposit of solid material on the walls of cooler C was noticed.

In the restarted experiment cooling was only applied to vessel R$^2$, the cooler C was not filled and the jacket was open to air. Under these cooling conditions plugging occurred again and this could be attributed to the pump. Due to a larger temperature difference over the pump-head section settling occurred. This settling hampered the flow through the pump and ultimately the flow stopped. Therefore, a fair comparison between the continuous-flow microwave reactor and the conventionally heated experiments could not yet be made.

Experiment B

Experiment A was repeated adopting the previous procedure. Instead of a membrane pump a gear pump was engaged in experiment B. Introduction of large particles relative to the tube-diameter led in this case also to plugging in the suction line. During the first period this plugging problem could be circumvented by slowly stirring the contents of vessel R$^2$. Suction occurred via the top. In this

way the reaction mixture was always saturated in substrate, although not completely homogeneously mixed with respect to the total composition.

The Laurydone process can be divided into three stages (see Figure 6.8): the start-up stage I, stage II of predominant esterification and stage III to remove the reaction product (water). Stage I is not appropriate for making a comparison between conventional and microwave heating.
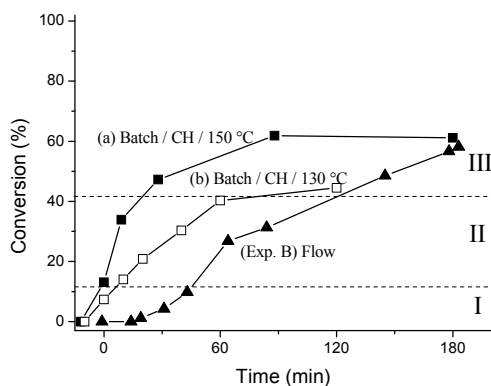


**Figure 6.8** *Esterification of (S)-pyroglutamic acid (10 wt%) with n-decanol in (Exp. B) continuous-flow experiment B in batch-loop mode, (a) conventionally heated batch experiment at 150 °C and (b) conventionally heated batch experiment at 130 °C.*

Microwave heating is much faster than oil-bath heating. For oil-bath heating it takes more than 10 min to reach the desired temperature. For the flow experiments heating is, however, almost instantaneous. In stage II the esterification is predominant at a constant temperature, making this stage suitable for a comparison. Stage III is dominated by the presence of water and the latter's rate of removal which controls the equilibrium in the esterification. Also the difference in setup plays a role in the removal of water, which appeared to be important (chapter 2.6).

For the batch experiment at 150 °C the conversion reached a plateau of 60 % after 90 minutes. The time-conversion history resulting from the microwave-heated run in the continuous-flow reactor operating in a batch-loop mode approaches this plateau approximately linearly. The batch-loop setup clearly has another influence on the removal of water than the batch operation. In the Laurydone synthesis comparing conversion rates of batch and flow processing is more complicated than in the cases of biocatalysis and racemization. A much higher temperature is measured outside the tubular reactor $R^1$ than in the other cases. As a consequence,

direct correction with the fractional residence time is insufficient due to the continuation of the esterification outside the tubular reactor $R^1$.

Therefore, to make an estimation for the rate in $R^1$, a correction has been applied with a combination of the fractional residence time *and* the reaction rate outside the tubular reactor $R^1$ based on batch (b), see entry 2, Table 6.5.

**Table 6.5**    *Conversion rates (interval of 13 and 42 % conversion) of the esterification of (S)-pyroglutamic acid under different reaction conditions.*

| entry | conditions | overall reaction rate [$\Delta$conv.min$^{-1}$] | fractional residence time[*] | relative reaction rate [$\Delta$conv.min$^{-1}$] |
|---|---|---|---|---|
| 1 | batch (a); 150 °C | *1.14* | *1* | *1.14* |
| 2 | batch (b); 130 °C | *0.51* | *1* | *0.51* |
| 3 | experiment B | *0.70* | *0.26* | *2.68* |
|   | *with correction* |  |  | *1.27**[**]* |

[*] *fractional residence time in the reactor compared to the total reaction time [based on the ratio of the volume of the microwave heated tubular reactor ($R^1$, 180 mL) per total reaction volume (700 mL); overall rate = $V_{R^1}/V_{tot} \cdot$ rate (MW, $R^1$).*

[**] $\left[ real\ rate\ (MW,\ R^1) \right] = V_{R^1}/V_{tot} \cdot \left( \left[ overall\ rate \right] - V_{R^2}/V_{tot} \cdot \left[ rate,\ (batch,\ 130°C) \right] \right)$; ($R^2$, 520 mL).

After correction of the overall reaction rates, Table 6.5 demonstrates almost identical behavior for batch or batch-loop operation by microwave heating. This is, however, only valid for stage II in the Laurydone process. The stages I and III are controlled by the heating rate and the experimental setup, respectively.

## 6.5 Aspirin synthesis

The examples of heterogeneous reactions studied so far in the Milestone FlowSynth demonstrated relatively long reaction times demanding for multiple passes through the microwave-heated tubular reactor to reach an acceptable conversion. To obtain a more complete picture of the performance of the FlowSynth also a homogeneous reaction has been selected, namely, the synthesis of aspirin (Scheme 6.4).
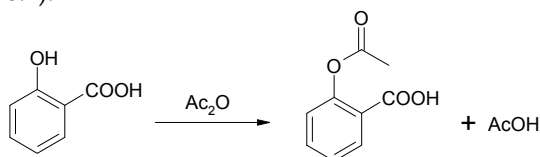


**Scheme 6.4**    *Synthesis of aspirin; O-acetylation of salicylic acid.*

The synthesis of aspirin proceeds by a relatively straightforward procedure and allows investigation of an intrinsically fast homogeneous reaction in a potentially single-pass operation (Scheme 6.4). So, the aspirin synthesis in the FlowSynth is a real continuous process.

Starting with a recipe based on a high concentration (25 wt%; 2.3 mol·L$^{-1}$) of salicylic acid in acetic acid, at which the substrate was completely dissolved at 50 °C, instantaneously led to plugging. Lowering the concentration of salicylic acid improved the handling in a continuous-flow mode, although reaction rates were negatively affected. Simultaneously, a switch from a gear pump to a membrane pump was necessary to ensure a stable flow (see Figure 6.1). After the first 150 mL of the product stream (R$^1$ = 180 mL) operation was at steady state. So residence time and conversion can be correlated at multiple points (Figure 6.9). The mean residence time (390 ± 39 s) was determined by measuring the volume of the product stream during 3 min process time. The measurement was repeated 20 times. Also the salicylic acid conversion (57 ± 4 %) was measured in these samples, see Figure 6.9.

The actual product stream shows a delay which is in accordance with the mean residence time (the sum of volume of tubing and cooling unit is approximately also 180 mL). The relatively longer residence times of fractions 9 and 13 are witnessed as relatively higher conversions at fractions 11 and 15, respectively.
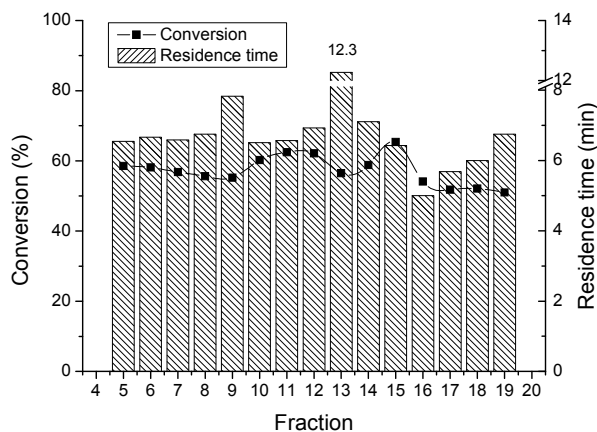


**Figure 6.9**    *Conversion profile of the aspirin synthesis in acetic acid (1 M) with 2 molar equivalents of acetic anhydride at 120 °C in a continuous-flow experiment. Volumes of the product stream during 3 min process time.*

Batch experimentation using microwave or conventional heating with an identical reaction time (390 s) resulted in conversions of 66 % and 64 %, respectively.

With the assumption that the O-acetylation of salicylic acid obeys approxiametely first order kinetics in the first part of the reaction, the reaction constant (k) can be estimated (see Equation 6.1). Together with the model, representing the tubular reactor R[1] as a series of CSTR's, the conversion ($x_A$) related to residence time can be calculated for the continuous-flow process (Equation 6.1). The total volume ($V_{total}$) of the tubular reactor R[1] is 180 mL and the flow rate ($\phi_v$) is 0.46 mL.s^{-1}. If the number (n) of equally sized tanks in series is 3 or 2 then the theoretical conversion would be 60 or 57 %, respectively; which perfectly agrees with the experimentally observed conversion (57 %).

**(6.1)**

$$x_A = 1 - \left( \frac{1}{1 + k \cdot \dfrac{V_{total}}{n \cdot \phi_v}} \right)^n$$

*k = 2.7·10⁻³ s⁻¹ [120 °C]*

$k = 2.7 \cdot 10^{-3}\ s^{-1}\ [120\ °C]$

The translation from batch to continuous processing appears to be a relatively simple procedure, although more knowledge (*e.g.* on the internal temperature of tubular reactor R[1]) is required to allow a reasonable prediction.

However, a longer residence time is not possible with the current setup. The reaction rate can be improved with a catalyst (see section 5.6). Complete conversion demands for a long mean residence time. Nevertheless, batch-loop operation allows high conversions in a short time with proper temperature control.

## 6.6 Discussion

The energy efficiencies of the performed reactions have been calculated in a similar way as reported in chapter 5.4. The results are collected in Table 6.6 and illustrate high yields for the transition from microwave energy to heating for the first three types of experiments.

**Table 6.6** *Efficiency of conversion from microwave energy to heat.*

| entry | experiment | description | efficiency (%) |
|---|---|---|---|
| 1 | biocatalysis | *exp. A; based on physical constants of toluene* | **89** |
| 2 | racemization | *exp. A; based on physical constants of p-xylene* | **88** |
| 3 | laurydone | *exp. B; based on physical constants of n-decanol* | **92** |
| 4 | aspirin | *based on physical constants of acetic acid* | **37** |

The aspirin synthesis with an extremely low flow rate demonstrates poor energy efficiency. For these low flow rates heat losses to the surroundings seem not to be negligible. The lowest efficiencies in chapter 5 were also found with the lowest flow rates.

All calculations in Table 6.7 are based on the heat capacity of the major component (*e.g.* solvent) present in the reaction mixture.

## 6.7 Conclusion

Aspects of scaling-up microwave-assisted reactions have been investigated and discussed to be possible, even without optimization. High production rates can be obtained for batchwise operation by numbering up the microwave heated reactor units.[6] The step to homogenous continuous-flow processing has been investigated also without further process research involving a fast reaction (*i.e.* aspirin synthesis).[4,10]

The results described in this chapter show the success of a straightforward translation from operation in stirred vessels on bench scale to operation in a loop system with a tubular microwave-heated reactor with respect to chemical performance in terms of conversion and selectivity. Furthermore, preservation of the microwave effect was observed for the heterogeneous racemization of (*S*)-*N*-acetylindoline-2-carboxylic acid. Conversely, handling and processing of heterogeneous reaction mixtures require more development work for the transfer from small-scale stirred batch reactors to a batch-loop or even a continuous operation. Redesigning the present FlowSynth setup allows to cope with issues such as solid and slurry handling.

Larger scale operation is expected to enable minimization of the obstacles (*e.g.* plugging) encountered in the experiments reported in this chapter.

From the perspective of safety or selectivity, rapid cooling and heating are easily achieved with the current FlowSynth equipment.

In summary, organic chemistry can be performed in a microwave-heated batch-loop system or a continuously operated tubular reactor configuration. Safety aspects and an easy, direct translation to continuous processing are two positive elements for the FlowSynth setup.

In specific cases a positive contribution (*i.e.* microwave effect, see chapters 3.3 and 4.4) is observed just as in small-scale batch processes. However, large acceleration of reactions is not expected by microwave heating under controlled reaction conditions.

## 6.8 Experimental section

*The continuous-flow reactor has been supplied by Milestone srl, Italy. The tubular reactor can either be equipped with a Teflon or a Weflon stirrer. The original setup includes a membrane pump of Alldos GmbH (now known under the name Grundfos); type 281-9,6-1004; 100 bar; 50 Hz. The gear pump has been supplied by the manufacturer Gather Industries, type 320; PM8060 L.*

*General Methods: Chiral gas chromatography (GC) was performed on a Shimadzu 6C-17A GC equipped with a Chrompack Chirasil-DEX CG (DF=0.25) column and a FID. Injection temperature was set at 250 °C and the detection temperature was set at 300 °C. Temperature programs were used to optimize the analysis for each reaction mixture, see each specific procedure. Tetradecane was used as an internal standard.*

**Biocatalysis**

*(R)-1-phenylethyl acetate. A 1L round-bottomed flask was charged with a solution of (R,S)-1-phenylethanol (48 g, 0.4 mol) and vinyl acetate (172.2 g, 2 mol) in toluene (700 L). The reaction mixture was circulated through the continuous-flow reactor of Milestone equipped with a Weflon stirrer via a membrane pump with a flow of 175 mL.min$^{-1}$ and heated to 70 °C ($T^1$). On top of the reactor cooling was applied to maintain $T^2$ below 30 °C. Subsequently, Novozym 435 (5.0 g) was added to the flask (experiment A) or to the tubular reactor (experiment B, including a temporary hold of the flow) and the set temperature was maintained for a period of 180 min. The total reaction volume was 940 mL. Average power usage during reaction was calculated to be 226 W (experiment A) and 236 W (experiment B), see Figures 6.10 and 6.11 for the reaction parameters of both experiments. During the reaction aliquots were taken from the liquid phase and measured by GC. After 180 min the mixture was collected, resampled and cooled.*

**Figure 6.10**    *Schematic overview of reaction parameters operational during experiment A of the biocatalytic esterification (pump and stirrer speeds are expressed in percentage in this figure).*
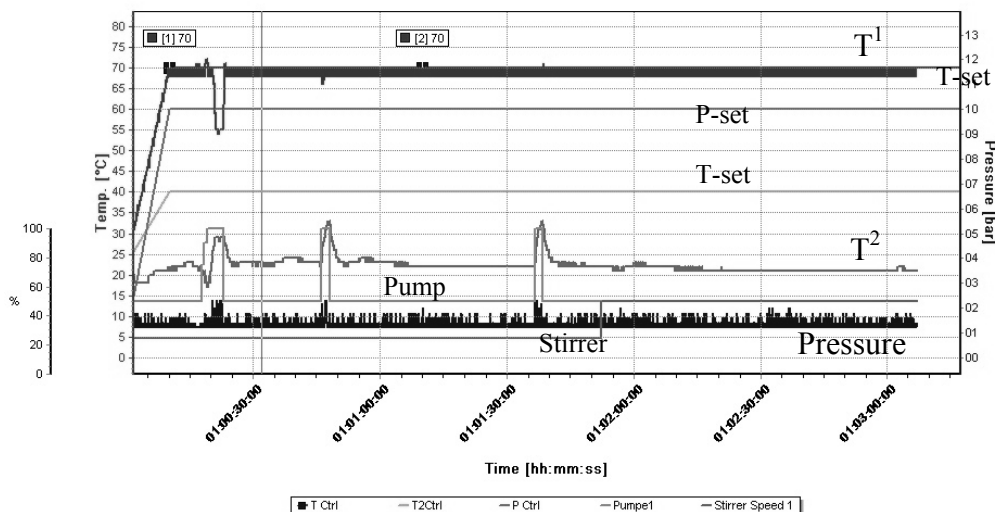


**Figure 6.11**    *Schematic overview of reaction parameters operational during experiment B of the biocatalytic esterification (pump and stirrer speeds are expressed in percentage in this figure).*
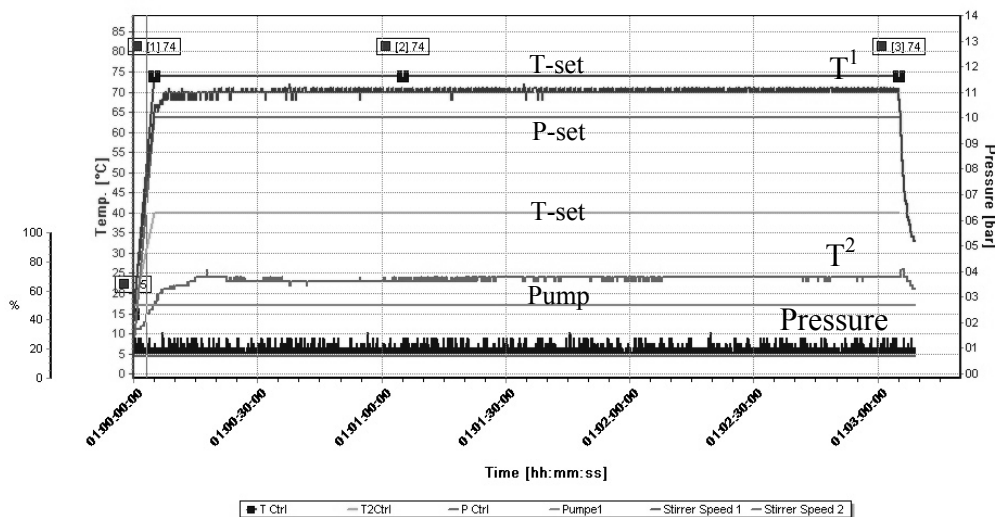
*Racemization*

***(R,S)-N-acetylindoline-2-carboxylic acid [exp. A];*** *A 2L round-bottomed flask was charged with dry (S)-N-acetylindoline-2-carboxylic acid (178 g, 0.87 mol, 99 %ee S) and p-xylene (679 g). The reaction mixture was circulated through the continuous-flow reactor of Milestone equipped with a Weflon stirrer via a membrane pump with a flow of 216 mL.min$^{-1}$ and heated to 130 °C (T$^1$). On top of the reactor cooling was applied. Subsequently, acetic anhydride (22.3 g, 0.22 mol) was added to the flask and the set temperature was maintained for a period of 263 min. The total reaction volume was 850 mL. Average power usage during reaction was calculated to be 407 W. During the reaction aliquots (~50 mg) were taken and quenched with water (25 μL) to neutralize the anhydride. The samples were dissolved in a mixture of formic acid (3 mL), isopropanol (25 mL) and n-hexane (72 mL) and analyzed by HPLC. Chiral column (Daicel, Chiracel OD) with an eluent composed of formic acid (1 v%), isopropanol (10 v%) and n-hexane (89 v%).*

***(R,S)-N-acetylindoline-2-carboxylic acid [exp. B];*** *A 2L round-bottomed flask was charged with dry (S)-N-acetylindoline-2-carboxylic acid (126 g, 0.62 mol, 99 %ee S) and p-xylene (650 g). The reaction mixture was circulated through the continuous-flow reactor of Milestone equipped with a Weflon stirrer via a membrane pump with a flow of 222 mL.min$^{-1}$ and heated to 130 °C (T$^1$). On top of the reactor <u>no</u> cooling was applied. Subsequently, acetic anhydride (14.8 g, 0.14 mol) was added to the flask and the set temperature was maintained for a period of 182 min. The total reaction volume was 785 mL. Average power usage during reaction was calculated to be 280 W, see Figure 6.12 for the reaction parameters. During the reaction aliquots (~50 mg) were taken and quenched with water (25 μL) to neutralize the anhydride. The samples were dissolved in a mixture of formic acid (3 mL), isopropanol (25 mL) and n-hexane (72 mL) and analyzed by HPLC. Chiral column (Daicel, Chiracel OD) with an eluent composed of formic acid (1 v%), isopropanol (10 v%) and n-hexane (89 v%).*
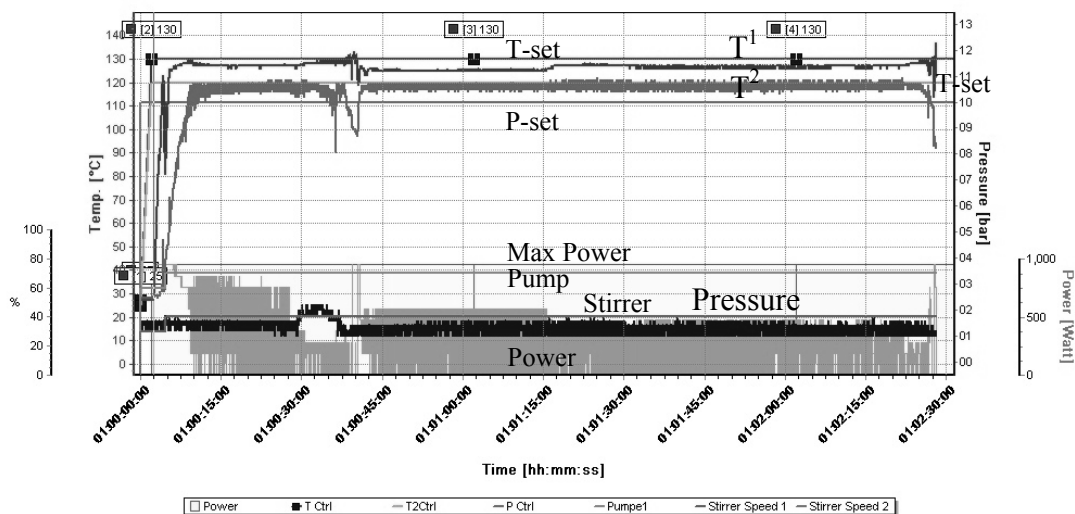
**Figure 6.12**    *Schematic overview of reaction parameters operational during experiment B of the racemization of (S)-N-acetylindoline-2-carboxylic acid.*

*Laurydone process*

*[exp. A]. A double-walled reactor was charged with (S)-pyroglutamic acid (69.1 g, 0.54 mol) and n-decanol (622 g, 3.93 mol). The reaction mixture was circulated through the continuous-flow reactor of Milestone equipped with a Weflon stirrer via a membrane pump with a flow of 115 mL.min⁻¹ and heated to 150 °C (T¹). On top of the reactor no cooling was applied. Double-walled reactor was thermostatic at 60°C at the walls. Reaction time was 140 min. The total reaction volume was 700 mL. Average power usage during reaction was calculated to be 294 W. During the reaction aliquots (~50 mg) were taken, quenched with dichloromethane (3 mL) and measured by ¹H-NMR (CD₃OD, 200 MHz), typical signals δ (ppm)  4.14 (t, 2H, CH₂-OCO, product), 3.53 (t, 2H, CH₂-OH, n-decanol).*

*[exp. B]. A double-walled reactor was charged with (S)-pyroglutamic acid (69.0 g, 0.53 mol) and n-decanol (622 g, 3.93 mol). The reaction mixture was circulated through the continuous-flow reactor of Milestone equipped with a Weflon stirrer via a gear pump with a flow of 343 mL.min⁻¹ and heated to 150 °C (T¹). On top of the reactor no cooling was applied. Double-walled reactor was not thermostatic at the walls. Reaction time was 178 min. The total reaction volume was 700 mL. Average power usage during reaction was calculated to be 444 W, see Figure 6.13 for the reaction parameters. During the reaction aliquots (~50 mg) were taken, quenched with dichloromethane (3 mL) and measured by ¹H-NMR (CD₃OD, 200 MHz), typical signals δ (ppm)  4.14 (t, 2H, CH₂-OCO, product), 3.53 (t, 2H, CH₂-OH, n-decanol).*

134
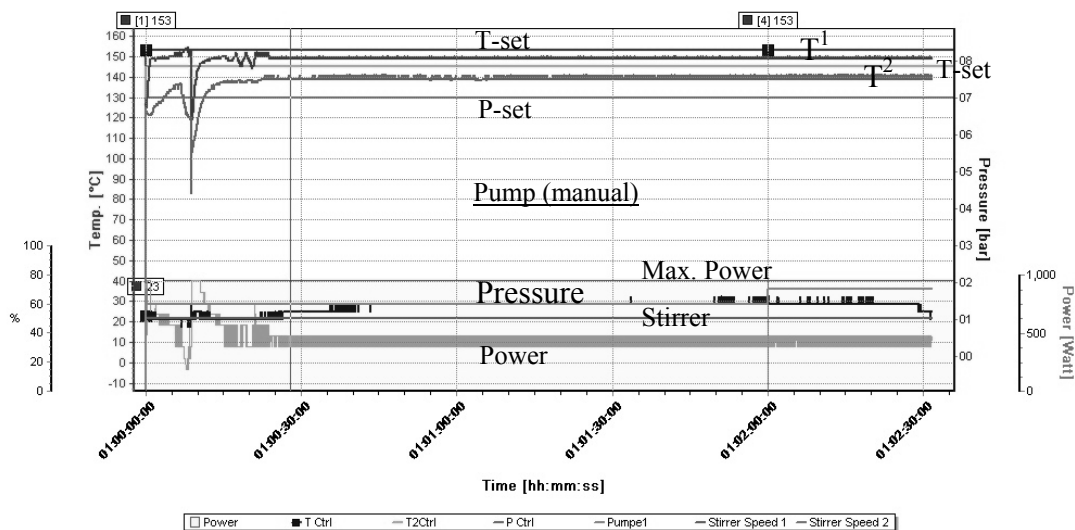
**Figure 6.13**　*Schematic overview of reaction parameters operational during experiment B of the synthesis of Laurydone.*

*Aspirin synthesis*

***O-Acetyl salicylic acid.*** *A 2L round-bottomed flask was charged with salicylic acid (207 g, 1.5 mol), acetic acid (1228 g, 1.12 L) and acetic anhydride (307 g, 3.0 mol). After 15 min of mixing (almost complete dissolution) the reaction mixture was pumped through the continuous-flow reactor of Milestone equipped with a Weflon stirrer via a membrane pump with a flow of 27 mL.min$^{-1}$ and heated to 120 °C (T$^1$). On top of the reactor cooling was applied. Residence time was 6.5 min. Average power usage during reaction was calculated to be 253 W. During the run the reaction mixture was collected in fractions, aliquots were taken, and measured by $^1$H-NMR (CD$_3$OD, 200 MHz), typical signals δ (ppm) 8.01 (d, 1H, CH-C-COOH, aspirin), 7.84 (d, 1H, CH-C-COOH, salicylic acid).*

## 6.9 References and notes

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# Concluding remarks and outlook

This thesis comprises many examples in which reaction performance with microwave heating was directly compared with that of conventional heating. This comparative study has led not only to a much better understanding of microwave-assisted chemistry, but also to recognizing the importance of proper control of the reaction parameters (*e.g.* temperature).

Microwave irradiation gives results identical to conventional heating for most of the studied reactions, provided that the temperature and stirring efficiency are controlled. Either the possibility of a high heating rate related to microwave heating or any variation in the temperature distribution, due to poor mixing, give rise to (uncontrolled) deviations. Rate enhancements by microwave heating are observed for certain heterogeneous reactions. Heterogeneity alone, however, is not sufficient to induce microwave effects. In particular, when the solubility of the substrate is very low and the absorbance of microwaves by the reaction medium is poor, microwave heating appears to be superior. On a microscopic scale absorbance of microwaves indirectly results in a higher reaction rate. Rate enhancements up to a factor of 9 have been registered. The magnitude of these microwave effects depends on the heterogeneity of the system. If the solubility of the reactant in such a reaction mixture is increased – by addition of a solvent or by selecting a better dissolving analogue of the same class of compounds – then the magnitude of the microwave effect decreases. When the reaction mixture becomes homogeneous the microwave effect has completely vanished. Therefore it is stated that, this rate-accelerating effect originates at the interphase of solid and liquid, due to a local higher temperature by selective microwave absorption leading to a local increase of solubility of the substrate and an increase of the global rate coefficient.

The batch-wise experiments were performed in a multi-mode apparatus which, from an energetic perspective, is generally less effective than a mono-mode microwave oven. An increasing power-density under smaller-sized experimental conditions apparently leads to higher reaction rates, due to the inability of accurate temperature control (partially based on the use of external or slow sensors).

In the field of automation of (parallel-)synthesis for small-sized vials (a few mL's), microwave heating has proven its value in the laboratory. Based on our observations with microwave heating further growth in high-throughput experimentation can be expected. Also for reactions performed at higher temperatures or pressures leading to large rate enhancements, a positive development is expected which allows the chemist to run several chemical reactions per day. Another field of interest for applying microwave heating is the fast production of larger volumes on a pilot-plant scale.

Importantly, flow chemistry, including micro-reactors, has aroused more interest in recent studies. Part of this development will be beneficial for the implementation of microwave heating in the production of larger quantities of chemical products. In our view, the best opportunities lie in continuous processing for scaling-up microwave-assisted chemistry, as a consequence of the limited penetration depth of microwaves. Once the continuously operated microwave-assisted chemistry has been demonstrated to be successful, the laboratory scale operation simplifies the procedure to produce material on a kg-scale by microwave irradiation.

The current FlowSynth as supplied by Milestone is a unique commercial device. For homogeneous, non-viscous reaction mixtures the setup of different components (including *e.g.* pump, tubing) can be operated on demand. The introduction of solids or more viscous solvents requires, however, some modifications to prevent clogging or fluctuating flow rates. Redesigning the tubular reactor towards a characteristic plug-flow reactor prefers the implementation of a static mixer (radial mixing). To control the performance, either multiple temperature sensors or the absence of a temperature profile over the length of the reactor are preferred. Otherwise a broad residence time distribution – representing the characteristics of a continuous stirred tank reactor, resulting in a uniform temperature – automatically implies a different geometrical (spherical) design. Increasing the volume to surface ratio, by scaling-up under limited penetration depth conditions, creates a better perspective to handle solids. Such a design reduces energy losses to the environment, thus preventing premature precipitation.

The technical feasibility of microwave heating on an industrial scale in fine chemical applications has been demonstrated by the Laurydone® process. The appearance of beneficial microwave effects in the presence of sparingly soluble substrates makes microwave heating even more promising if the added value is confirmed. From a more realistic perspective, the use of microwave equipment and operational costs as such are not competitive compared to conventional heating by steam or oil. Compensation by sufficient rate enhancements, increased selectivity and process safety aspects is needed to overcome this hurdle. However, a growing interest in flow chemistry combined with further development of large magnetrons (*i.e.* providing microwave power on the spot) might induce successful implementation. Recent developments generating effective microwave heating, even in large-scale batch reactors or drying equipment advertised by Püschner GMBH in Germany and an Ukranian institute (SSI NAS), are promising. Best chances for application are reactions requiring fast heating rates or processes which benefit from selective heating (*e.g.* two phases). High heating rates refer to kg-scale productions in the early stages of product development, where time is more important than costs. In 2009 the company Cambrex Inc has already reported successes in producing pilot-plant quantities (*e.g.* a Pd-catalyzed continuous microwave-heated process).

Common for the research magnetrons is a frequency of 2.45 GHz. Further investigations have to provide an answer to the question which frequency is the best for large-scale fine chemical operations.

# ___Summary___

### Microwave heating in fine chemical applications: role of heterogeneity

Only since 1986, microwave-assisted chemistry has been taken up by the academic world. So far, microwave technology is mainly used to efficiently synthesize lead compounds on a gram scale. The pharmaceutical industry, however, is responsible for the largest part of the development of microwave-assisted chemistry, by producing more compounds in a shorter time span with the aid of an automated microwave-heated setup (*e.g.* high-throughput experimentation). Primarily, microwave irradiation heats up reaction mixtures.

In chapter 1 an overview of the real and apparent successes of microwave technology is given. In the subsequent chapters the following main topics have been addressed. The first part of the research was focused on the superior value of microwave heating with respect to the conventional approach in chemical conversions. Its origin is, to a considerable extent, based on the published claims regarding rate-accelerating microwave effects. A second part deals with the implementation of the gained knowledge in scaling-up particular fine chemical processes. In a third part a conceptual design was elaborated in which the microwave oven has been incorporated in a fume-hood setup to produce larger quantities of product on a commercial scale.

In chapter 2, aimed at reproducing reactions from literature, a consistent approach has been selected to compare microwave heating with conventional heating. This has revealed the true nature of the observed microwave effects. The biocatalyzed reactions were given extra attention in view of claimed synergetic effects, where – besides reactivity – also enantioselectivity and stability were considered. All of these biocatalyzed (trans)esterification studies with three types of enzymes (Novozym 435, Subtilisin, PPL) have demonstrated identical time - conversion profiles for both heating methods. The cyclization to piperidines and piperazines from the corresponding halides neither revealed rate accelerations with microwave heating. During these conversions the formed hydrogen halide was actively removed by applying thermal energy or by neutralization with base. The oxidation of benzyl alcohol to benzaldehyde with iron trinitrate revealed to be a complicated process of redox - reactions giving an identical result when subjected to microwave irradiation in contrast to literature claims. The same observation holds for the tri-alkylation of methyl gallate where the conversion rate was not influenced, despite the heterogeneity due to a large amount of solid reactant ($K_2CO_3$). Most illustrative was the microwave effect observed in the Laurydone® process (esterification of pyroglutamic acid with *n*-decanol) revealing the importance of agitation to reproducibly compare heating experiments. Here, the originally observed microwave effect (factor 3) vanished by proper agitation. Although in this case, the use of microwave energy to heat the reaction was superfluous, the feasibility of scaling-up the Laurydone® process to an industrially relevant scale was demonstrated. For all mentioned reactions in chapter 2, temperature control proved to be crucial to judge whether any favourable microwave effect is present.

In chapter 3 the racemization of two types of *N*-acetylated amino acids (*N*-acetyl-phenylalanine and *N*-acetylindoline-2-carboxylic acid) was investigated. Solubility of the substrate in *p*-xylene is poor and the acetic anhydride mediated reaction is accelerated up to a factor 8 by microwave heating.

A comparable approach has been followed in chapter 4 to study the beneficial influence of microwave irradiation on the mono-addition of a series of C6-substituted (methyl, ethyl, isopropyl and phenyl) isocytosines to hexamethylenediisocyanate. The heterogeneous reaction mixture gives also rise to a microwave-enhanced reaction rate up to a factor of 9. A change in the substituent influences not only the reactivity, but also the solubility and by that the magnitude of the microwave effect. This accelerating effect finds it origin at the interphase of solid and liquid where local microwave absorption occurs. Locally higher temperature induces a locally increased solubility of the substrate and so an increase of the global rate coefficient. The microwave effect completely vanishes when a solvent was added (chapter 3) or decreases when the solubility of the substrate improves (chapter 4). In summary, heterogeneous reactions may display an added value in the conversion rate by microwave heating.

In chapter 5 the necessity is described to switch from batch-wise to continuous operation when applying microwave heating, due to the limited penetration depth of microwaves. To broaden the operational window of a flow-reactor with respect to moderate reaction rates, a recycle loop system has been introduced. Although the incorporation of a microwave oven implies higher costs in acquisition and in operation compared to conventional heating, the usage is advantageous regarding practical performance and safety. The FlowSynth® reactor of Milestone corresponds to a series of three continuous stirred tank reactors on average.

In chapter 6 four examples are discussed to demonstrate the actual performance of the FlowSynth® under different operational conditions. An *O*-acetylation of salicylic acid (aspirin-synthesis) was conducted in a single pass under homogeneous conditions. Three heterogeneous reactions (a biocatalyzed esterification, a neat esterification and a racemization) are performed applying a recycle loop (*i.e.* batch-loop operation). Although plugging appeared to be an important obstacle with heterogeneous mixtures, a relatively direct translation from batch-wise operation to continuous processing has been demonstrated. Moreover, the beneficial microwave effect, in case of the racemization as mentioned in chapter 3, was maintained in the FlowSynth®.

In the epilogue our results are put in a wider perspective. Further developments of microwave technology in combination with industrial possibilities have been discussed.

In my view microwave heating is only innovative when its principle of selective heating is actively pursued.

# ___*Samenvatting*___

Pas vanaf 1986 werd magnetronchemie in academisch onderzoek toegepast. Magnetrontechnologie is tot nu toe vooral gebruikt om efficiënter nieuwe teststoffen op gramschaal te synthetiseren. Voornamelijk op het gebied van automatisering van experimenten binnen de farmaceutische industrie heeft magnetronchemie zich sterk ontwikkeld, omdat meer experimenten in een kortere tijd dan met conventionele verwarming kunnen worden uitgevoerd. Het primaire doel bij de toepassing van magnetronstraling is om reactiemengsels te verwarmen.

De stand van zaken in de toepassing magnetronchemie wordt toegelicht in hoofdstuk 1. In de resterende hoofdstukken worden de volgende onderwerpen behandeld. In het eerste deel wordt het onderzoek beschreven hoe magnetronverwarming chemische omzettingen versnelt ten opzichte van conventionele verwarming. Hiervoor is de aanzet voor een groot deel te vinden in de vele publicaties met claims betreffende reactieversnellende magnetron-effecten. In het tweede deel is de opgedane kennis van de magnetronverwarming toegepast bij het opschalen van fijnchemische processen. In het laatste deel wordt beschreven hoe magnetronverwarming is ondergebracht in een zuurkastconcept voor (continue) productie van fijnchemicaliën op commerciële schaal.

In hoofdstuk 2 zijn voornamelijk reacties uit de literatuur getracht te reproduceren. Consequent is voor iedere eerder beschreven chemische reactie de vergelijking tussen magnetron en conventionele verwarming uitgezocht. Dit heeft geleid tot een logische verklaring voor de waargenomen magnetroneffecten. De biogekatalyseerde reacties zijn hierbij uitgebreid onderzocht. De enantioselectiviteit en stabiliteit zijn twee aspecten naast de reactiviteit die zijn meegenomen in het vergelijkend onderzoek. In de verestering en omestering met drie types enzymen (Novozym 435, Subtilisin, PPL) zijn identieke reactiesnelheden gevonden wanneer beide verwarmingsmethoden werden vergeleken. Bij de vorming van piperidines en piperazines uit de overeenkomstige halides, waarbij het gevormde HX actief (via base of thermisch) werd verwijderd, was geen versnelling te zien bij gebruik van magnetronstraling. De oxidatie van benzyl alcohol tot benzaldehyde met behulp van ijzer trinitraat bleek een complex proces van redox reacties te zijn waarbij geen magnetroneffecten werden gevonden in tegenstelling tot een claim in de literatuur. Bij de tri-alkylering van methyl gallaat werd eveneens de conversiesnelheid niet gewijzigd door gebruik van de magnetron, ondanks het heterogene karakter van deze reactie (overmaat $K_2CO_3$). Het meest illustratieve voorbeeld van een magnetroneffect bleek het Laurydone proces (verestering van pyroglutaminezuur met *n*-decanol) te bieden. Ten aanzien van de geïmiteerde eerdere claim van een gunstig magnetroneffect bleek hier de menging van de reactanten van cruciaal belang te bieden. Een goede menging deed het oorspronkelijk waargenomen magnetroneffect met een factor 3 volledig verdwijnen. Hoewel in dit geval het gebruik van de magnetron geen toegevoegde waarde in de conversie bleek te hebben, is desondanks aangetoond dat de opschaling van het Laurydone® proces met magnetronstraling als zodanig toch van relevante industriële betekenis is geweest. Voor alle

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reacties die in hoofdstuk 2 beschreven zijn blijkt een betrouwbare temperatuursmeting van wezenlijk belang te zijn om te kunnen beoordelen of voordelige magnetroneffecten echt kunnen worden waargenomen.

Hoofdstuk 3 behelst de racemisatie van twee geacetyleerde aminozuren (*N*-acetyl-fenylalanine en *N*-acetylindoline-2-carbonzuur). Het substraat lost in *p*-xyleen beperkt op en de door azijnzuur anhydride bevorderde reactie wordt versneld in de magnetron (tot een factor 8). In hoofdstuk 4 is een soortgelijke benadering beschreven waarbij eveneens magnetronstraling een gunstig effect heeft op de enkelvoudige additie van een serie C6-gesubstitueerde (methyl, ethyl, isopropyl en fenyl) isocytosines aan hexamethyleendi-isocyanaat. Ook hier leidt heterogeniteit van de substraten tot conversies met magnetroneffecten (tot een factor 9). Verandering van substituent beïnvloedt niet alleen de reactiviteit, maar ook de oplosbaarheid en daardoor de grootte van de magnetroneffecten. Lokale absorptie van magnetronstraling in de grenslaag van de vaste en vloeibare fase leidt indirect tot een verbeterde conversiesnelheid. Een verhoogde lokale temperatuur leidend tot een toegenomen oplosbaarheid ligt hieraan ten grondslag. Het magnetroneffect verdwijnt helemaal indien een oplosmiddel wordt toegevoegd (hoofdstuk 3) of vermindert indien de oplosbaarheid van het substraat toeneemt (hoofdstuk 4). Resumerend, heterogene reacties kunnen een positieve bijdrage leveren aan de reactiesnelheid bij gebruik van magnetronstraling.

In hoofdstuk 5 wordt de noodzaak toegelicht om, bij toepassing van magnetronstraling, van een batchgewijze procesvoering over te schakelen naar een continu proces vanwege de geringe penetratiediepte. De introductie van een recycle stroom maakt het tevens mogelijk om reacties met een lagere conversiesnelheid in een doorstroomreactor uit te kunnen voeren. Hoewel verwarming met de magnetron duurder is (in gebruik en in aanschaf) dan de conventionele verwarmingstechnieken zoals stoom en olie, zijn er toch voordelen te behalen vanuit een praktisch oogpunt en veiligheid. Verdere karakterisering van de gebruikte FlowSynth® doorstroomreactor van Milestone toonde aan dat de reactor zich laat bedrijven als een cascade van gemiddeld 3 even grote CSTR's.
In hoofdstuk 6 wordt aan de hand van een viertal voorbeelden beschreven hoe de doorstroomreactor onder verschillende omstandigheden presteert. Bij de homogene acetylering (aspirine synthese) werd de productstroom in porties opgevangen na één enkele passage. Drie heterogenene reacties (een biogekatalyseerde verestering, een autogekata-lyseerde verestering en een racemisatie) zijn uitgevoerd met een recyclestroom. Hoewel verstopping bij heterogene reacties een belangrijk obstakel bleek te zijn, kan een relatief eenvoudige vertaalslag vanuit een batchgewijze naar een continue procesvoering worden aangetoond. Tevens is de meerwaarde van magnetronverwarming in geval van de racemisatie - zoals besproken in hoofdstuk 3 - ook bevestigd bij gebruik van de FlowSynth.

De resultaten zijn in een breder perspectief geplaatst in een epiloog, waarin de verdere ontwikkelingen van magnetrontechnologie en de industriële slaagkans zijn aangegeven.

Naar mijn mening is magnetrontechnologie alleen innovatief als het principe van selectieve opwarming ingezet wordt.

# *Curriculum vitae*

Mark Dressen is geboren op 17 augustus 1979 te Heerlen. In 1997 behaalde hij zijn VWO diploma aan SG St. Michiel te Geleen. Opeenvolgend startte hij met de Hoger Laboratorium Opleiding aan de Hogeschool Zuyd te Heerlen met organische chemie als afstudeerrichting. De bijbehorende stage- en afstudeeropdracht zijn volbracht binnen de "Lead Discovery Unit" van Organon N.V. te Oss in 2001. In hetzelfde jaar is hij begonnen als chemicus binnen de R&D afdeling van DSM Pharmaceutical Products te Venlo. Procesontwikkeling en –verbetering waren de kerntaken van de projectmatige werkzaamheden voor meerdere locaties. In 2005 is er door hem bewust de keuze gemaakt om zijn passie voor magnetronchemie om te zetten in een promotie in de onderzoekseenheid "Applied Organic Chemistry" in de groep "Molecular Science & Technology" van de Technische Universiteit Eindhoven, onder leiding van eerste promotor prof. dr. L.A. Hulshof, tweede promotor prof. dr. J. Meuldijk en co-promotor dr. J. A. J. M. Vekemans. De belangrijkste resultaten van dit onderzoek staan beschreven in dit proefschrift; "Microwave heating in fine chemical applications: role of heterogeneity".

Mark Dressen was born on August 17th 1979 in Heerlen, the Netherlands. In 1997 he received his degree in secondary education at SG St. Michiel in Geleen, the Netherlands. As a follow up he started the "Hoger Laboratorium Opleiding" at Hogeschool Zuyd in Heerlen with organic chemistry (BSc) as specialization. He completed his external traineeship with the Lead Discovery Unit of Organon N.V. in Oss, the Netherlands. In the same year he started as a chemist in the R&D department of DSM Pharmaceutical Products in Venlo, the Netherlands. The key-tasks of this project-based assignment, located at multiple locations, were process development and improvement. In 2005 an intentional decision was made to start his PhD research, based on his passion for microwave-assisted chemistry, within the research unit of Applied Organic Chemistry as part of the group Molecular Science & Technology at Eindhoven University of Technology, under the supervision of prof. dr. L.A. Hulshof, prof. dr. J. Meuldijk and dr. J. A. J. M. Vekemans. The most important results of this research are presented in this thesis; "Microwave heating in fine chemical applications: role of heterogeneity".

# *Dankwoord*

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